—THE—

Untoward Effects of Drugs.

A Pharmacological and Clinical Manual.

—BY—

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SECOND EDITION, REVISED AND ENLARGED.

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PREFACE.

Occupying, as it does, a middle ground between pure experimentation and empiricism, the science of materia medica is enriched alike from the laboratory and observations at the sick bed. It is through a combination of the results furnished through these two channels, that the typical modus operandi of any individual drug can alone be determined.

There occur, however, now and then, in the therapeutical application of certain drugs, certain deviations from this typical, and, to a degree, normal action, the correct perception and significance of which are not always understood. But a knowledge of these is of the utmost importance to the physician, as affording him an explanation of the causes of certain symptoms, and also furnishing him with a guide to his practical management of them.

The records of the individual facts here indicated—the appearance of abnormal effects of drugs—are scattered throughout the most diverse parts of medical literature, and are either not at all or but superficially considered in the manuals or text-books of materia medica. For this reason I have for a long time been making a collection of these facts, examining them critically, and making additions to this collection from my own personal experience. I have presented the results of this labor in this book in the hope that they will meet a practical want, and at the same time stimulate others to further observations in the same direction.

L. LEWIN.

BERLIN, January, 1881.

TRANSLATOR'S PREFACE.

When I saw the announcement of Dr. Lewin's book on "Die Nebenwirkungen der Arzneimittel," I was constrained from experience, both in private practice and in the capacity of teacher of materia medica and therapeutics, to send for a copy. The necessity of a treatise on the subject indicated by this title must have been felt by all practitioners, for previous to the appearance of this book by Dr. Lewin there was no systematic work of this nature, such information as was extant existing merely as it was scattered in occasional references in text books and periodical literature. An examination of the work so convinced me of its great value as to induce me to undertake the translation herewith presented, the author's consent having been previously obtained. I am under obligations to Dr. Lewin for his review of the proof sheets and his endorsement of the translation. He has also made copious additions to the original, so that the book as it now appears in English is virtually a second and revised edition.

J. J. MULHERON.

Detroit, Mich., December. 1882.

INTRODUCTION.

§ 1

Medicines exert a localized influence in the animal economy, *i. e.*, they influence, according to their chemical or physical properties, certain classes of cells or cellular tissue, chiefly or exclusively. "Certain substances are possessed of an affinity for specific parts of the system." From this fundamental view, first enunciated by Virchow,* it follows that a whole series of remedies may, in addition to their curative effects, give rise to symptoms, either by direct or through reflex action upon similar or dissimilar groups of cells, which should not have been occasioned in securing the therapeutic effects of the remedy. In this way, in the exhibition of opiates, for instance, are not only the nerve centres and nerves affected, but also the peripheral nervous structure, and there follows in consequence, in addition to the more or less pronounced hypnotic effects of the drug, a transitory impairment of the motor nerve supply of the intestines, and through this, constipation. In the case of tartar emetic, given internally, vomiting occurs in consequence of irritation of the mucous lining of the stomach, but the drug, through its direct effect on the cardiac tissue, causes also a simultaneous reduction in the force of the heart's action. When chloroform is given by inhalation we have a direct action on the cerebro-spinal nerve centres, but particularly on the cerebrum; at the same time we have a checking of the heart's action through reflex action aroused by local contact of the drug on the mucous lining of the air passages. While, therefore, under the influence of opium and chloroform, similar nerve substance in different parts of the body suffers change, the antimony in tartar

* Virchow, Specificer, und Specifisches, Archiv. für patholog. Anatomie, Bd VI., 1854, p. 24.

emetic affects tissue of a heterogeneous nature, as mucous membrane and muscular tissue. In an analogous manner may substances possessed of an inherent property of influencing a still greater variety of cellular formations, induce a corresponding complexity of pathological conditions. But in spite of this these operations are regarded as physiological, inasmuch as they are inseparable from each other and are inherent as a whole to the medicine employed. The individual symptoms are differentiated, in respect to the claim of therapeutic action, only in so far as a distinction is made between the characteristic action and untoward effects induced.

§ 2

While nearly all the various medicinal agents, and in the manner indicated, exert their typical inherent action on certain groups of cells, each group, respectively, being a focus of disease, and thus act therapeutically, it is not infrequently evident that in individual cases the desired localized action does not obtain, the drug being in this regard inert. Thus chloroform may fail to exert its hypnotic action, quinine to reduce an enlarged spleen, and purgatives, even such as are classed as drastics, to induce catharsis.

When the drug is up to the recognized standard as regards its active principle—which must be assured in such cases—this important abnormality, in a therapeutic sense, can only be referred to the person in whom it is noted, whose organization or the nature of whose diseased or healthy parts which it is desired to influence, must present differences from corresponding parts in other individuals. This same postulate may be predicated concerning such persons as present peculiarities of predisposition to certain diseases, and who consequently are, for instance, not susceptible to the contagious diseases *e. g.*, typhoid fever, and so on. In such cases the immunity need not reside in any grossly anomalous condition, but may, as will be indicated in detail further on, be referred to textural and organic variations which are still physiological.

It is manifest that if certain organs of individual persons behave in a peculiar manner, as regards medicines, the rule of whose action is to work definitely determined effects, thera-

peutic experiments with such substances in such individuals, are liable to lead to false conclusions. We have in this fact a possible explanation of the diametrically opposite effects which have been frequently observed to follow one and the same drug in different persons.

§ 3

Of far greater importance to the physician than the failure of the drug to work its normal action, are the untoward effects which medicines have not infrequently been observed to induce, effects which are either substituted for the normal action or appear simultaneously with it. As an illustration of such untoward action may be noted the eruption following the administration of quinine, or in rare cases the undue effect of the same drug on the organs of sight, as seen in long continued amaurosis. Cod liver oil, ordinarily so bland, may give rise to a vesicular eruption, iodide of potassium may occasion a hypersecretion from the mucous membrane of the eyes and nose, and salicylic acid may, among other effects, cause diaphoresis and nervous disturbances.

The greatest variety of names may be found in medical literature for these untoward symptoms following the exhibition of drugs. In Germany they have been and still are known as "Nebenwirkungen," "physiologische Nebenwirkungen," or "Arzneisymptome" and are also spoken of as the "special" or "accidental" or "peculiar" action of the drug. French authors refer to them as "Inconvénients" or "Inconvénients thérapeutiques," as "Accidents" or "Cas d'accidents." In England they are occasionally termed "unpleasant symptoms."

There has been some hesitation in regarding these "nebenwirkungen" as poisonous effects. And very properly so, for we are not justified in regarding one or more symptoms as the effects of a poison, simply because they may not occur in 999 cases and yet appear in the thousandth. In addition to this it may be noted that the majority of these untoward effects do not, in any particular, correspond with the symptoms induced by a poisonous dose of the drug, and that we cannot, at will, effect these untoward symptoms and especially such as manifest themselves in cutaneous eruptions. These occur only under

very definite individual conditions and can not, therefore, be always excited through experimentation. There is, even to-day, no lack of physicians who, still imbued with old time views on humoral pathology, ascribe the occurrence of these untoward effects of drugs to certain teleological conditions, even as they were formerly wont, in like manner, to regard hæmorrhoidal fluxes. Just as it was regarded as a fortunate circumstance that the "vital principle" controlling the blood vessels, chose the hæmorrhoidal vessels through which to eliminate the "impurities"* so the untoward effects of medicines, especially those manifesting themselves on the skin, were regarded as the evidences of a struggle going on between the medicine and the "disease elements" in the body, and more particularly in the blood, functional changes, or material anatomical lesions in which latter were an evidence of either the suppression or elimination of such "elements" from the body. As opposed to this vitalistic humoral pathology we have another theory on which to account for these untoward effects, both such as manifest themselves as almost constant attendants on drug action and those which occur but seldom. *The cause of these may reside in the individual, be due to circumstances of time and place, or be referable to the inherent nature of the remedy.* We shall now consider the former of these causes.

§ 4

The natural peculiarity of each individual in respect to all others may be either permanent or but temporary. It manifests itself most markedly as the result of the manifold adventitious circumstances which are the usual causes of disease.

The same external conditions, operating on a number of persons, may produce such a variety of results, that while some may not be appreciably affected by them others may suffer transient effects, and still others sustain permanent functional derangement. Here there is evidently a wide range of individual susceptibility to external influences. This susceptibility may even become so marked, that causes which inherently operate within physiological limits may be productive of pathological symptoms. The odor of the rose, the eating of a strawberry,

*Refer. b. O. Schuetz, Die Lehre von der Constitution. Berlin, 1872.

etc., may in some excite certain nervous symptoms, palpable cutaneous eruptions, for instance—a behavior which has been regarded as a heightened individual irritability, or as an idiosyncrasy—while innumerable other persons will be in no wise thus affected.

Analogous phenomena manifest themselves as a result of the external or internal exhibition of medicines. The extract of calabar bean instilled into the eye excites only in certain persons a burning sensation in the conjunctival sac, and an increased secretion of tears; morphia taken internally causes only in excitable persons a spasm of accommodation; and pilocarpin, in certain persons and in certain doses, excites profuse diaphoresis, literally bathing the individual in perspiration, while in others, similar doses scarcely excite a slight transpiration. We thus see, under conditions otherwise similar, variations in the operation of external influences on similar tissues, which find their explanation only in the peculiarity of the individual.

But of what nature are these? We are not yet in a position to give an entirely satisfactory answer to this question. It is only recently* that an attempt has been made, through comparative anatomical examination of the physical behavior of certain organs, as the heart, blood vessels, intestines, etc., in persons of different ages and sexes to explain so-called constitutional differences. Efforts have also been made, through experiment, to throw light upon this obscure subject. Thus Albertoni† found in the effects of atropine on young dogs, an analogue to the observation that children, of from fifteen months to five years of age, may take with impunity doses of the tincture of belladonna which would give rise to many symptoms of poisoning in adults. In the young dog 0.01 to 0.02 gramme (gr. $\frac{1}{6}$ to gr. $\frac{1}{3}$) of atropine causes no disturbance of intelligence, but only a trifling indisposition and slight excitement, while in older animals there is marked disturbance of the intelligence. He discovers the reason of this discrepancy in the difference in the degree of development and excitability of the nervous system which exists between the young and

*Beneke, Die Anatomischen Grundlagen der Constitutions anomalien. Marburg 1878. —Veröffentlichungen der Gesellschaft für Heilkunde in Berlin, IV., 1881, p. 10.

†Albertoni Archiv. f. exper. Pathologie XV. p. 264.

the adult animal. The experiments of Soltmann* may be adduced in support of this view. This observer found that in dogs ten days old electrical irritation of the cortex of the brain produced no effect, and that the inhibitory apparatus of the heart in newly born dogs is either not at all or but imperfectly developed. The latter is demonstrated by the fact that electrical irritation of the vagus causes no stoppage, or at most but a slight decrease in the frequency of the cardiac contractions. The electrical excitability of the motor nerves is also less in the new-born than in adults.

There are further, as we shall see later on, a series of physiological processes in the body which, under certain circumstances, may give it the character of specific predisposition, and we are familiar with pathological conditions so insignificant in their nature as not to be cognizable during life, which may, however, render the individual highly susceptible to irritation. But do all of these circumstances suffice to explain what Virchow has termed the "mystery of individuality?" Certainly not. And if we consider but a few of the details which may come under notice here, if we, for instance, recall the limitless variability in the vascular supply of the system, the variety of the arrangement of glandular tissue in the glands, the discrepancies of innervation in individual organs, the differences in the size of their filaments in the majority of individual nerves, and the diversity of arrangement of the coarser and the finer fibers in corresponding muscles in different persons, we must confess that we have in these facts, instances not only of the unknown but also of the unknowable. But we are not justified, on account of this, in denying general individuality, or in belittling its significance. For the possibility of explaining is, as Virchow demonstrates, not yet a scientific criterion, inasmuch as we know much empirically for which we can find no warrant in reason. No exact investigation, be it anatomical or physiological, pathological or therapeutical, has as yet been able to lift the veil spread over the conditions of individual peculiarity. It has in all ages been regarded as the privilege of only the most favored geniuses or of the most prolonged experience, to arrive at that delicate insight which

*Soltmann Jahrbuch f. Kinderheilkunde IX. 1875, XI. 1877 und XII Heft 1.

permits of an approximate conception of the specific character of the individual.

The fact that since the establishment of practical and descriptive medicine, peculiarities of constitution have been recognized and considered, is too well known to necessitate mention. The doctrine of temperaments, the conception of a sanguine, choleric, phlegmatic, and melancholic constitution under the belief that these were severally dependent on a predominance of blood, bile, mucus and black bile in the individual, remained for centuries a firm conviction amid the wreck of all other medical theories; though this doctrine, the quintessence of humoral pathology, is most one-sided and falsely based, it is nevertheless in perfect harmony with all attempts to arrive at a knowledge of minute individual peculiarities.

The factors which present themselves in connection with the latter question cannot be of a gross nature. This has an especial bearing on the specific peculiarities of individual organs. And if there is aught to support the declaration of Virchow,* that "the reaction of the tissues does not essentially depend upon external influences but directly on their internal disposition," it is the individual peculiarities which the tissues of certain persons evince in regard to medicines. The external application of tincture of iodine to the skin ordinarily gives rise to but an erythema, and yet there are persons in whom an application of the same preparation produces blisters and extensive œdema. Even a bland ointment composed of any pleasant fresh fat excites inflammatory action when rubbed into the skin of many persons. In such cases the cause can only reside in some very slight, but chemically and physically inexplicable, idiosyncrasy of the skin and its parts. When the diversity of the chemical and physical relations of isomeric bodies *i. e.*, bodies containing an equal percentage of elements, are taken into consideration the difficulty of tracing such grave functional disturbances to such slight deviations in the arrangement and construction of the organ concerned is readily overcome. In such cases by a mere change in the disposition of certain molecules, so great changes are produced in the body that

*Virchow, Krankheitswesen und Krankheitsursache, Arch. für pathol. Anat, Bd. 79, H. 1, p. 10.

they appear as elementary differences. In spite of this the number of carbon, hydrogen and oxygen atoms, as for instance in pyrogallic acid and phloroglucin, and in hydrochinon, resorcin and brenzcatechin remains the same. Perhaps we may be led to recall through this the behavior of allotropic bodies, which probably reveal, through but slight variations in molecular arrangement of entirely similar chemical constituents, very diverse physical properties, as is seen in carbon in the forms of diamond, graphite and coal.

We can conceive of certain organs of the bodies of a group of persons, being so arranged by nature that although entirely similar in chemical constitution and even in microscopical texture, they are still so different that they react under the slightest irritation, or evince an unwonted reaction in the presence of ordinary stimulation.

§ 5

We have hitherto considered only individuals, or organs in their variable relations to all others of a similar kind. Although the differences which have been noted, are very marked, they will nevertheless be found to be exceeded *by those which are manifested by similar and dissimilar organs of the same person as the result of the external, specifically medicinal influence*, whether resulting directly through the action of the drug or as a result of indirect, reflex action. There is even a difference in the physiological capability of individual organs of similar nature in the same body. The degree of contractility of the gastrocnemius of one side is rarely found under similar external conditions to be equal to that of the opposite side, nor is the irritability of a nerve identical with that of its correspondent. The cause of this difference may be found in existing inherent differences of development of the functional elements of the parts, one muscle thus containing more primitive fibres than the other, and the one nerve being endowed with more nerve fibres than its fellow of the opposite side; it may also result from a greater or less degree of perfection in the several parts. The latter property is noticeable in a comparison of the muscles of the extremities of the more greatly exercised right side with those of the left.

It is further a noticeable fact that similar but not corresponding portions of the body, as for instance different group of muscles, in the same manner differ in their functional activities, without being diseased. In accordance with this fact a given volume of the deltoid muscle exceeds in mechanical executive ability a similar volume of the intercostal muscles.

We know that while the cardiac branches of the pneumogastric can be irritated only by a very strong current the pulmonary branches of the same nerve are endowed with an unusual degree of irritability. These differences are still more marked in apparatuses made up of different tissues, as for instance, the joints. One is at first inclined to believe that there exists a complete correspondence between the arrangement of individual parts, and a similarity in their reaction against external impressions. This, however, is not the case. In precisely the same manner such intimate complexity of arrangement as obtains in the instance cited—muscles, connective tissue, cartilage and bone—in the most varied proportions, and revealing the greatest differences with regard to the extent of their vascular and nerve supply, are not to be placed side by side and are certainly not to be held as of equal value. This is most clearly manifest in any effort which may be made to secure identical effects in these parts with the same drug, when they are disturbed by disease. In such cases the most unexpected results follow the most direct application. An observation by Senator* is very instructive in this connection. He found that in the employment of carbolic acid by direct injection into the joints in acute articular rheumatism, the most favorable effects were apparent in the shoulder joint, then respectively in the knee, wrist, elbow, and last of all in the hip joints. In the discussion of this fact Senator adduces the following as important in occasioning these peculiar conditions: anatomical differences, the number and disposition of the vessels, or only unknown peculiarities in the structure of the joints, without, however, deciding in favor of any one of them. There are, indeed, so many possibilities which suggest themselves in this connection, and we are so far from understanding the most insignificant

*Senator, Berl. Klin. Wochenschr., 1876, p. 70.

of them that we are obliged to content ourselves with bringing them as completely as possible within the range of our observation. But even if in a particular case, we had proved, for instance, an abnormal vascular distribution in the right shoulder joint as compared with that of the left corresponding joint, or a more perfect innervation of the knee-joint than appears in the elbow, we could even then but conjecture why the same medicine applied to these parts produces different results, why in one person it operates therapeutically and in another produces effects exactly opposite.

A further investigation in this direction shows us that in persons, happily few, with a special predisposition, the effects of a drug, whether desirable or undesirable, appear so simultaneously in different parts, and occur so closely together, that it is impossible to separate the one from the other. We know of instances in which the exhibition of iodide of potassium for the reduction of hypertrophied (hyperplastic) glands, as for instance the thyroid or cervical, etc., while producing the desired effects has also unhappily caused a serious atrophy of glands which had hitherto been perfectly sound, *e. g.*, the mammæ and testes. Such a change can, however, in our opinion, only be brought about in organs which, although they appear normal, have nevertheless essentially departed from the normal standard. A merely slight departure from the normal standard may subject them to influences to which they are not ordinarily subject.

§ 6.

The differences in the reaction of certain persons or individual tissues of the same organism against certain medicinal influences, which we have been considering in the foregoing pages, reside in an organic constitutional tendency, which is either congenital or acquired, and is unalterable.

There exists, however, a disposition which is but temporary. This may have its foundation either in a greater abundance in the system of chemical substances which cause an unusually prompt solution of the medicines introduced, or which may unite with them to form injurious compounds, or it may be conditioned on pre-

existing pathological changes in the organs, to wit, diseases of the inhibitory apparatus of the system.

With regard to the former we shall consider the striking observations of Mialhe.* He explains the abnormal reaction on medicines, due to the difference in the mixture of animal juices, rather as a "chemical idiosyncrasy" than as an "idiopathic idiosyncrasy," which is to be regarded as the expression of differences in tissue construction. It is, for instance, known that under certain circumstances insoluble medicines, as oxide of iron, zinc, Kermes mineral, etc., excite effects in the system quite different from those which usually follow the administration of these substances—they excite baneful untoward effects. The cause of this is to be found in excessive acidity of the stomach, through which larger quanties of the drugs named are dissolved. This difference in fluids which may be regarded as the expression of local disturbances, is very intrinsically distinct from inherent humoral pathological dyscrasia, in that it is quite temporary and may be obviated by the employment of chemical or dietetic means.

The consideration of such condition of the stomach renders it easy in a given case to understand the action of a particular drug. Until even the present time, for instance, opinions are divided as to the reason why the much used basic nitrate of bismuth, the old magisterium bismuth, and sometimes even in small doses, occasions violent irritation of the stomach and bowels, as vomiting, diarrhœa, etc., and also general disturbance, while in other cases large doses, 4 to 6 grammes, produce no abnormal effects. It has been conclusively proved that the reiterated assertion that these untoward effects are due to the lead or arsenic in the bismuth can not be true, the quantities thus contained being usually too small. A much more common cause is to be found in the undue quantity of the acids of the stomach. When these exceed the normal it may be due to a change of an innocuous basic salt into a corrosive neutral substance, or through the action of water on the latter into a poisonous acid salt, and thus, through absorption of the metal, causing local as well as general poisonous effects. That the

*Mialhe, Die Receptirkunst, übers. von Biefel. Breslau. 1852, page 239.

stomach may at different times, dependent on the individuality of particular persons, the nutriment ingested, the state of digestion, etc., contain different amounts of acids, is a fact which can be so easily established, both clinically and experimentally, as scarcely to require further mention.

The same is true of the intestinal juices. The greater or lesser alkalinity of these involves the solubility of a great range of mineral and vegetable substances, and in the presence of but a slightly alkaline reaction the action of a drug may be entirely suspended or it may be but partially operative, or through an excessive alkalinity in the intestinal juices so great a quantity of the drug exhibited may be dissolved as to cause a modification of the effects usually observed. The latter effects may for instance, be noticed in the exhibition of the yellow sulphuret of antimony. While usually only a very mild expectorant action is observed, there are cases in which the full and pure action of antimony, vomiting, diarrhœa, and cardiac sedation are noted. The cause of this is only referable to increased alkalinity of the intestines through which a larger portion of the drug is rendered absorbable.

The chloride of sodium present in the system exerts an influence fully as marked as do the acidity of the stomach and alkalinity of the intestines, and it is even more variable in its quantity. When, for instance, calomel is exhibited, a difference in its effects on individual functions is observable, according to the quantity of common salt which may be present in the system. In patients who have for a long time been on low, possibly saltless diet, calomel has scarcely any action, inasmuch as a great part of the chloride has been, as it were, washed out of the system by means of fluid diet and large quantities which have been given to drink. On the other hand, as Mialhe has observed, persons who have long subsisted on salted food, sailors for instance, are very susceptible to calomel, the drug being liable to cause in them symptoms of intestinal irritation and a series of other unpleasant effects of mercury.

From these few facts, briefly stated, it will be seen that many untoward effects are liable to attend the exhibition of medicines. In most cases no peculiarity of constitutional tendency is requisite. Pathological changes in the stomach and

bowels, and also febrile conditions, which modify the composition of the secretions of these organs, and even the unconscious ingestion of some article of diet which forms deleterious compounds with certain drugs, are liable to induce a predisposition to untoward effects not contemplated.

While changes may thus take place in different parts of the body in which the necessary conditions exist for the formation of tissue change, certain organs may at the time of the administration of a particular drug be in such a pathological condition, how slight soever this condition may be, existing changes may be temporarily aggravated by the medicine, or new pathological symptoms may develop in the organ, which might not otherwise have supervened. A few examples may be given in illustration of this. It is known that potassic iodide is partially eliminated through the mucous lining of the air passages and that it thus occasionally gives rise to slight catarrhal symptoms, which, not being very decided, disappear on suspension of the drug. If, however, lesions exist coincidently with the action of the iodide of potassium, it may, as has been at different times observed, especially in syphilitics with laryngeal ulceration, give rise to œdema of the glottis which may speedily prove fatal. In the same manner very small doses of active cathartics, as elaterium, gamboge, etc., which if they cause irritation of the intestines, do so within limits which are to a degree physiological and but temporary, may, when there is a previously existing abnormal condition of the mucous membrane, excite a severe inflammatory condition of the tract, with tenesmus, bloody stools, etc. Should the causative connection between such effects of the medicine and the existing slight organic changes not be understood, the new conditions thus induced may be mistaken for a spontaneous disease of the portion of the body attacked.

It is scarcely necessary to note that such conditions as menstruation, pregnancy, mental excitement, and intellectual exertion, insomnia, and even abstinence and digestion which may be within physiological limits, are capable of modifying in various ways the action of medicines.

§ 7.

The third cause of a transitory predisposition to abnormal action of medicines lies in disturbed regulation. Should any other cause of disease attack a particular part of the body, there arises a disturbance indicated by Schütz, on the strength of views enunciated by Virchow: "But this disturbance is not pathological should the regulation be easy. It is only when the regulation is difficult or impossible that danger is liable to supervene." The favorable or deleterious action of remedial agents is also dependent on a good or bad regulation. The latter is here to be regarded as identical with elimination. Ordinarily calomel, for instance, in proper doses induces by its action on the intestines, purgation. As soon as this occurs the greater part of the drug is discharged from the body with the feces, in the form of mercuric sulphide. Should, however, purgation from any cause not occur the calomel may remain in the intestines, chiefly in the cæcum, where by continuous contact with chloride of sodium it is changed into corrosive sublimate and thus cause injurious corrosion and ulceration of the intestinal mucous lining.

Should the regulation be normal, or, more strictly, should the secretory apparatus properly perform its function, even poisonous substances may be for a long time ingested without causing any disturbance—while if any of the excretory ducts are closed poisonous symptoms immediately supervene. Hermann † has utilized this fact in explaining the intermittent symptoms of lead poisoning. He gives utterance to the opinion that "while the lead cachexia must be regarded as the effect of the diffusion of certain portions of lead in the body, the additional affections must have a specific cause which in spite of further developing lead poisoning, may finally disappear. This cause he detects in a transitory increase in the quantity of lead in the system, due either to increase in the supply or diminished elimination. He calls that condition of saturnism, in which lead constantly circulates throughout the body and in which the supply and elimination counterbalance

†Hermann, Archiv. f. Anat. u. Physiologie, 1867, p. 64 und Lehrbuch der Toxicologie, Berlin, 1874, p. 205.

each other, "the state of compensation." We can thus understand how "any momentary disturbance of the function through which lead is eliminated from the body is followed by an increased quantity of lead in the system and the consequent development of new symptoms, which the ordinary supply of lead could not account for." Thus is also explained how many persons manifest an apparent immunity from the poisonous effects of lead, while others are seriously affected by very small quantities. It has been demonstrated that certain other medicines may give rise to undesirable untoward symptoms, when the excretory apparatus is diseased and thus but imperfectly discharges its functions. Thus Chauvet showed that while in the healthy person, from a half to a third of the sulphate of quinine ingested is eliminated, only from a fiftieth to a tenth is excreted in patients suffering from interstitial nephritis. The bromide of potassium, which is ordinarily eliminated at the latest in twenty days, is not excreted under thirty or thirty-five days in cases of kidney disease. It is probably in this manner that some of the untoward effects following the external application of iodoform are produced, and particularly when, as in the treatment of wounds, carbolic acid has been previously employed, the latter drug, as has been demonstrated, being prone to cause irritation of the kidneys. It is not necessary that the excretory ducts undergo pathological change, for even within physiological limits the functions of organs may be suspended, as may be seen in the case of the kidneys. Variations in the temperature are followed by variations in the quantity of urinary secretion and vicarious increase or diminution of perspiration. Thus is perhaps explained the fact that lead colic occurs most frequently during the hot summer months, when the quantity of urine voided is so markedly reduced and the perspiration correspondingly increased.

§ 8

In order to properly understand certain abnormal effects of medicines, it is necessary to consider, in addition to the causes indicated, that inherent property known *as habituation.* We know that psychical impressions within the broadest limits, from the strongest desire to the intensest disgust, from the highest

pleasure to the deepest sorrow, when their action is long continued, gradually lose their influence. We become accustomed to them, and the measure of their effect, the subjective manifestations, which are commonly aroused by them become gradually less and less and finally disappear altogether. We may assume that in such cases the centres of sensation are, through repeated excitation, deprived of their energy, *i. e.*, they no longer respond to ordinary impressions. The conduct of tissue, muscle, for instance, under repeated electric currents, affords an illustration of the fact here stated. Let the muscle be caused to contract through frequent irritation of the nerve and this contraction reaches its maximum of force at the beginning, to be followed by a condition of fatigue. This condition will continue until the muscle is afforded rest, that is time to get rid of those products of waste which the exertion has induced.

Precisely similar results may be reached by habituating one's self to a succession of doses of medicines and drugs. Instances of persons inuring themselves to certain poisons are afforded us in ancient history. Thus we are told that Mithridates having gradually accustomed himself to each of the then known poisons to such an extent that he could take large quantities with impunity, was finally unable to find a poison with which to commit suicide. This somewhat extravagant statement is, however, supported by what we see in our day of the effects of such active agents as alcohol, arsenic, opium and morphia in particular individuals. The quantities of these substances which are taken with apparent impunity, through a gradual increase of the dose, are frequently from ten to twenty times as large as would suffice to produce fatal effects in persons not thus inured. Some substances, also, as many of the class of laxatives and diuretics, are of such a nature that their habitual use ultimately deprives them of all pharmacological activity. Early in their employment their effect may be secured by increase of dose, but eventually even this does not suffice. We are familiar with these facts in the case, among others, of rhubarb, castor oil, the neutral salts, acetate of potash, squills, etc.

How are these peculiarities to be explained? Granted that

a given substance affects certain groups of cells, and we may expect a normal result from the action of that substance in the majority of instances : sleep will follow the use of morphia and catharsis the exhibition of rhubarb. As, however, a long continued electrical current when passed through a nerve or muscle will induce material changes in the same, exhausting its excitability, so will certain medicines similarly affect the tissues. The only difference between the two cases is that whereas the muscles and nerves are very quickly restored upon the removal of the electric current, either through rapid elimination of the matter decomposed by the current, or by a prompt replacement with new supplies, in the case of the medicine restitution is effected only after a complete removal of the disturbing factor from the part affected. But since it requires some considerable time to wholly eliminate these drugs from the body, each new dose is almost sure to overtake some remaining particles of the preceding dose, and thus the affected tissue is to a degree kept under the constant and unintermitting, exciting or benumbing influence of the drug. Inasmuch as there is thus no relaxation in the part its excitability is impaired, or in other words, a physiological or artificial excitant will fail to longer call forth any adequate reaction. Each further augmentation of the dose will, it is true, excite temporary reaction, but the excitability will only continue until it has again been dulled. A suspension of the substance may be followed by complete restitution, and in time the parts again respond normally to the action of the drug.

The foregoing affords an insight into the possibility of one's accustoming himself to the action of poisons. The gradually increased exhibition of these will induce inactivity in those groups of cells which are especially affected by them—they are still susceptible to passive, vegetative impressions, but are no longer capable of distinct, independent functional activity. The poison in excessive doses affects the inert texture in a manner identical with the action of the first small dose on normal tissue.

A poisonous action may, however, supervene after the person has been inured to the deleterious agent, as when the dose

has been so much increased as to attack the vegetative life of the tissue, and thus destroy its existence.

But this is not the only manner in which untoward effects may supervene in the course of the habitual use of a medicine. It is comprehensible, from the intimate connection between individual tissues, how organs whose functions are similar, are apt to be influenced by causes which operate upon any one of them. It is in this manner that a permanent affection of the brain and spinal cord may induce an alteration or disturbance in the peripheral nerves, in the heart's functions, etc. Hence we notice in those who are addicted to the opium habit that not only are there more or less severe cerebral symptoms but also disturbances in the functions of digestion, respiration, etc. Withdraw the disturbing medicinal agent, and we have symptoms pointing to disturbances of the equilibrium which has been created between the functions of different organs. The most characteristic of these symptoms is the craving felt for the drug which has been withheld. This feeling, reminds one of the desire for salt, when he has for any considerable length of time been deprived of it. Just as salt is an essential ingredient of the system and cannot be dispensed with, so has the medicine which has been withdrawn become through its long continued, accustomed employment an integral part of certain tissues, and its absence will be as keenly felt as the absence of an elementary constituent of the body.

The foregoing considerations are necessary to facilitate our understanding of many of the abnormal effects which are occasionally noticed to follow the exhibition of certain drugs. It is plain enough, for instance, that when a given part of the central nervous system has been lowered in its normal functional activity by continued use of some substance operating on it, the effect of any other substance which arouses it to action must be abnormal. This latter substance will either not act at all, or it will act perversely. An instance of this is seen in the effects of opiates in drunkards, particularly when attacked by delirium tremens, and those of chloroform in the same class of individuals. The skin may also become accustomed to certain drugs, which generally excite inflammation. It is a familiar fact, for instance, that in many persons the application of petro-

leum to the skin causes a vesicular eruption, which lasts for several days. Should the article be reapplied after the skin has been restored, the anticipated symptoms of inflammation may not appear. The condition may, however, be such as to require several inunctions to accustom the tissues of the skin to the irritation.

§ 9.

The season, time of day and part of the world in which a medicine is given are also factors of no mean importance in determining the abnormal effects of medicines, which it becomes us to consider. *The influences of time and place*, which are generally so little taken into account, have an undoubted effect in modifying if not indeed in determining many of the specific peculiarities of men. Hence the old schools, as Virchow* points out, regarded man attentively as to time and took into special consideration also the "epidemic constitution." It is certainly a fact that many of the morbific influences produce their effects only in certain localities and vary in their force and consequences on the body, with variations in time. If then the individual is thus affected by external influences it is comprehensible how certain medicines may, in a like manner, be made to produce abnormal or at leasts lightly abnormal effects. Careful, practical observation has revealed differences of action in individual drugs referable to the causes mentioned. Charvet† found that the effects of opium varied with the time of day, the climate and the race of the individual taking it. Thus the negro and Malay under the influence of opium manifest symptoms of convulsions, delirium and insanity, to which the Caucasian is not liable. Physicians have frequently noted similar discrepancies in the English colonies. According to the observations of Lisfranc, the medicinal effects of the chloride of barium are very variable, inhabitants of southern latitudes being able to tolerate larger doses than those of the north.

These facts, whose number might be largely increased, merit a fuller consideration by physicians, inasmuch as there is much, even though groundless skepticism regarding them. We are convinced that by a careful scrutiny of certain effects of medicines, in relation to the views above given, a large number of examples of similar divergencies could be added to those detailed.

*Virchow, l. c. Bd. VI., p. 29.

†Charvet. Die Wirkungen des Opiums auf d e thierische Oeconomie.—Leipzig, 1827.

§ 10.

In considering the diminished and deleterious effects of drugs, the fact must also be taken into consideration that the cause may also reside *in the drug itself*. The failure to secure the desired effect of a drug, or the untoward effect of a drug or pharmaceutical preparation, is more frequently attributable to the drug itself than is generally known or credited. The causes of this may be various. *Either the remedy (and this is particularly the case with vegetable drugs) in its raw state, as put on the market, although pure, is of an inferior grade, or if originally of good quality has through long storage lost its virtue, or the medicinal part has been mixed with foreign ingredients. Sometimes, too, the medicine is modified in its efficiency by the method of its preparation.*

It must be particularly borne in mind that in special cases the physical or chemical distinction between good and bad drugs is often difficult, and sometimes really impossible, and that likewise, particularly in the case of medicines of vegetable and animal origin, a very thorough study is necessary to qualify one for an opinion on this point which shall be of any value.

The activity of drugs may likewise be conditioned on their habitat. The respective commercial values of the different varieties of opium, aloes, colocynth, etc., are dependent on the countries whence they are derived, and this is generally the best criterion of the worth or worthlessness of the article. The difference in the effects of different varieties is sometimes remarkable. While, for instance, the 0.06 to 0.12 gramme (1 to 2 grains) of Socotrine aloes is sufficient to bring about a free evacuation of the bowels, the same effect can scarcely be secured by a dose of Arabian or Moka aloes of five times this size. Many of our indigenous plants present similar variations. Thus digitalis growing wild on hills is much more active than that which is grown in the valley, or cultivated. Hemp, as grown in this country, does not furnish the haschisch which is yielded by the hemp grown in warmer latitudes, and the hemlock which in this country yields coniin, is devoid of that principle when grown in Scotland. The nature of the soil, atmospheric temperature, season of the year, etc., are all so many factors in determining variations in the activity of medicinal plants. The

importance of the latter factor is particularly noticeable in many of our more active plants, as has been fixed by definite observations. We know that even the mountain digitalis, gathered in the mountain ranges of central Germany, differs in its pharmacological properties with the season of the year in which the leaves are picked. It is most active when the plant is in full bloom and at the acme of its vigor. The same is true of colchicin, it having been demonstrated* that the root or seeds which are gathered when the plant is in full bloom, contain the largest percentage of colchicin and are the most active. The most marked instance of changes, as regards the active principles of plants, is furnished in the case of momordica elaterium. The juice of this drug when collected in July, yields from 4 to 5 per cent. of elaterin; that from the fruit gathered in August, yields but about 0.69 per cent., while the juice of the squirting cucumber picked in September, is almost, if not entirely destitute of this principle. These facts explain the apparent contradictions in some of the older authors regarding the activity of medicinal doses of elaterium. It follows, from the fact stated, that 0.24 gramme (gr. jv) of elaterium from the juice of the fruit gathered in July, is equally as effective as about 1.5 gramme (gr. xxjv) of the August product, while doses of 4 grammes (℥ j) and more, of elaterium prepared from the September fruit, produces hardly any appreciable effect.

Many drugs also undergo change through long storage, developing in some instances new and not infrequently deleterious properties, through desiccation and the oxidizing influence of the air. If, for instance, in the preparation of extract of hyoscyamus dried instead of recently gathered leaves are employed, the product will be found to contain scarcely any hyoscyamus, while the same quantity of fresh leaves will yield a decided per centage. Ergot will lose its virtue unless carefully dried and closely sealed. But it is in the pomegranate root bark that the most decided changes in its activity due to such causes are noticeable. While the freshly gathered root is a reliable anthelmintic it is not only no longer active, but becomes an irritant emetic and disturbs digestion when old. A better and more careful manipulation and preservation than has been or is yet, in the opinion of experts (Fachmännern), cus-

*Schroff, Zeitschrift der Wiener Aerzte, Jahrg. 7, Bd. 1., 1851.

tomary, would doubtless have saved many drugs, especially of vegetable origin, from the fate of rejection as obsolete by the medical profession.

Very many vegetable and other organic as well as inorganic combinations are susceptible to change under the influence of the atmosphere. It is well-known that under such conditions a variety of deleterious products of chlorine are generated in chloroform. According to French authors the emetic action of morphia is due to a partial transformation into apomorphia, and it has been shown* that Fowler's solution loses arsenious acid in course of time, probably under the influence of organic matter which has found its way into it. The acid is reduced and escapes as arseniuretted hydrogen gas. The loss may in this manner be very considerable.

A further possible cause of the occurrence of change of action may reside in the fact that the drugs are mixed with foreign ingredients, and thus sold are employed by the dispenser. It has been asserted on the authority of an expert† that drugs in themselves of indifferent activity may be found to be adulterated with belladonna, hellebore, etc., which, although present in very minute proportions, necessitate great care and intimate familiarity with the subject in order that serious consequences may be averted. Finally, in so far as the purity of the drug is concerned, we know that the therapeutic activity, as also the objectionable properties of a variety of vegetable alkaloids,—aconitin, digitalin, etc., as also other chemical combinations—are largely conditioned on the methods of their preparation.

As opposed to variability in the effects of drugs detailed above, attributable to the quality of the preparation employed, are those certain effects which are due to the improper forms in which they are given. Thus we note loss of appetite, gastric oppression, diarrhœa, etc., in short the symptoms of catarrhal change, which occasionaly supervene on the exhibition in the form of powder, of substances which cause irritation through adhesion of their minute particles to the mucous lining of the alimentary tract. The administration of tannin, among other

*Bretet, Journal de Pharm. et Chimie. October, 1879. Page 355.
†Mayer, Pharmaceutische Centralhalle, 29. Juli, 1880.

drugs, in the form of powder, is not infrequently followed by such symptoms. In this manner the exhibition of irritating drugs in capsules, may set up functional disturbances in the stomach and bowels.

§ 11.

A contemplation of the conditions above enumerated which are liable to induce injurious untoward effects from drugs, will convince one both of their great variety and of the necessity which exists of a thorough knowledge of them. It is true, as a general rule, that no permanent impairment of function is thus caused; and yet there are many conditions under which such permanent change and even death may ensue. It is evident that these considerations are vested with an importance, by no means insignificant *from a medico-legal point of view;* and as a matter of fact the literature of this country, as well as that of other countries, furnishes abundant evidence corroborating this importance. There are cases on record in which a therapeutic procedure, conducted *secundem artem* has been attended by results sufficiently disastrous to bring the attending physician before a court of law, and this in spite of the fact that the same procedure had previously been frequently resorted to by others. When, for instance, after an enema of a solution of carbolic acid, through some idiosyncrasy of the patient the amount absorbed proves fatal, or when, notwithstanding the purity of the drug, a patient dies in the early stage of the administration of chloroform, the cases should be regarded as accidents for which no one can be held to account. The same is true of many other medicines whose administration, under certain circumstances, is followed by disastrous effects. There are well authenticated cases on record in which death in children has followed the employment of 0.006 and even 0.0007 gramme (grain $\frac{1}{10}$ to $\frac{1}{100}$) of opium. Were blame to be attached to the physician in such case, he could never prescribe such drugs except under a sense of grave personal danger. The surest safeguard against the possibility of such responsibility would seem to lie in the widest possible publicity of such accidents, thereby placing at our disposal a greater amount of information in reference to them than is now available.

§ 12.

It now remains for us to glance at the manner in which the principal of the untoward effects of individual drugs recorded in the literature of the subject, are produced. They may occur either by direct action or through reflex influence. It is only in a very few cases that we are able to determine with absolute certainty, in which of these two methods these effects are induced. This is partially conditioned on the manner in which a given medicine is applied and on the method of its elimination from the body. Thus irritating substances given by the stomach may exert an abnormal influence on the intestines, and establish a gastro-intestinal catarrh with its train of consequences. But there may also, as, for instance, in the case of the antimonial preparations, be set up a reflex influence on the heart from the local changes induced in the stomach. This does not preclude the possibility of a direct effect, through absorption, of the antimonial on the heart's action; as a matter of fact it sometimes suffers change in just this manner.

It is also conceivable that in consequence of irritation caused by a drug in the intestines or the larger bile ducts, a pathological condition may, through reflex action, be engendered in the skin. It is known* that other foreign irritating substances, such as the proglottides of tapeworm, or biliary calculi may through reflex action cause an eruption resembling urticaria. In an analogous manner many material changes occur in other points at which medicines are applied, as the subcutaneous cellular tissue, the mucous membrane of the eye, the bladder or the rectum from which reflex functional disturbances are set up in other organs, and, finally, while the substance is circulating in the blood phenomena may present, which are different from those which are primarily local and reflex. In this manner, for instance, the instillation of atropia may give rise to conjunctivitis, which by reflex influence causes photophobia. But should the drug be absorbed through its entrance into the lachrymal ducts symptoms of general poisoning may supervene. In general, however, so exact a differentiation is not possible.

*Litten, Dermatologische Beobachtungen, Charité-Annalen, IV., 1878, p. 194.

As regards the influence which the manner in which a drug is eliminated, may have in determining its untoward action, it may be stated that, dependent on the individuality of the patient, effects may be noted in the greatest variety of organs. We are familiar with a number of drugs which never select other avenues of elimination than the intestines and kidneys when given internally, and which select the latter channel when applied externally or given subcutaneously. There are, however, also others, antimony for example, which when applied externally are first discharged through the stomach and bowels where they set up pathological changes. It now only remains to mention those drugs which ordinarily leave the system with the urine, but which under any of the abnormal individual conditions detailed in the preceding paragraphs, after their ingestion select the skin as the place of their exit, and which may be detected therein by chemical means. The iodide and the bromide of potassium and arsenic are with others to be classed in this category. Others, as iodine, may after their injection into serous cavities be eliminated through the stomach.

Should the drugs exhibited vary in their strength—as they usually do—they are liable to exert either an irritating or a paralyzing action on the channels through which they are eliminated.

The chief efforts at explaining the manner in which pathological conditions follow drugs, have been made through the changes in the skin which have been found to follow the internal administration of some of them. To look for the cause in one direction, as is now and then done, is, however, apt to lead to error. It is certain that these conditions may occur in a variety of ways, and are not due exclusively either to direct irritation of the glands of the skin or of the connective tissue layer, through reflex action, through change in the vessels, or to an influence on the cutaneous nerves.

In all cases it is the drug as such which is the exciting cause of the changes induced in the skin, and that whether exhibited in very large or minimal doses. For it is most characteristic of individuality and the specific disposition which is conditioned on it, that influences of what kind soever, which are otherwise inoperative, may manifest themselves by intensifying different changes in individual organs. For this reason the unsupported

hypothesis* that it is not the drug itself, but the quite hypothetical substances which are formed by it in the blood, which, in certain cases, causes the pathological condition of the skin, is to be rejected.

The form of a given drug exanthem may not only differ in different persons, but may also vary greatly in the same individual. The differences here indicated are to be regarded as the expression of individual peculiarities or as dependent on the structure of the skin in different parts of the body.

The origin of the symptoms which reveal themselves in the organs of special sense as well as in other parts of the body, as a result of the exhibition of certain drugs, is discussed more in detail in the special chapters of this work.

*Behrend, Berliner Klin. Wochenschrift, 1879, No. 43.

TONICS.

FERRUM.

A variety of untoward effects referable more particularly to the digestive tract, are liable to manifest themselves in the course of the continued use of ferruginous preparations. It is not infrequently noted, in persons having normal digestive powers, that the exhibition of preparations of iron in somewhat increased and prolonged doses, and even the ferruginous waters, is followed by disturbance of digestion, diminution of appetite, gastric oppression and vomiting; and these results are particularly liable to follow when the drug is taken on an empty stomach. Defecation is retarded and the stools are blackened by a sulphuret of iron. More recent observations have demonstrated the ferrous salts to be better tolerated than the ferric. Ferrum redactum, the phosphate and the pyrophosphate of iron are said to disturb digestion but slightly. On the other hand the salts with organic acids (lactate, citrate, and acetate of iron) interfere very much with peptonization.

In very rare cases hemorrhages are said to occur from the mucous membranes. A more common result, according to Trousseau,* in healthy persons, and particularly in females, is an acne occurring on the face, the breast and back, which runs its course without febrile disturbance.

The teeth are blackened during the continued use of iron by a coating of the sulphuret of iron. It is necessary for this result that there should be a generation of sulphuretted hydrogen, either from carious teeth or through decomposition of secretions. The iron, which is held in solution by alkaline secretions of the mouth, is promptly precipitated by the gas. When the teeth are perfectly sound, blackening may still occur through the ingestion of food or drinks containing tannin, a tannate of iron (ink) being formed.

*Trousseau, Gaz. Médic. de Paris, 1843, No. 12.

The external application of the sesquichloride of iron as a styptic is very often attended by pain in the wound, owing to a defect in the preparation employed. When the iron salt contains no free hydrochloric acid, pain is nearly always absent. When pain is caused by a proper preparation, although it is severe it soon ceases. What is true in this regard of the preparation in substance is also true of the styptic cotton of commerce.

In order to make the sesquichloride of iron more easy of administration and to correct the sharp sour taste, which dilution with water does not overcome, Hager* recommends a mixture of the drug with glycerine or syrup, and its dilution immediately before taking with cow's milk. By so doing it is claimed that the teeth are not attacked, and that the taste of the iron is covered.

QUININE.

It has been claimed that the evil effects which supervene on the exhibition of quinine are due to a saturation of the system with the drug. It has been established, however, by the frequent occurrence of these accidents after the exhibition of but one medium dose, that there must exist in those who are thus affected a certain susceptibility to this particular action of quinine. It has even been shown by King,† on the strength of an observation of this nature, that this individual predisposition to injurious effects of certain drugs, as in this case of quinine, may be hereditary.

Organs differing most widely in their nature are influenced by quinine in this manner, and manifest pathological changes. The following symptoms are observed as indicating disturbance which it causes of the central nervous system: headache, deafness, general muscular irritability, with chilliness and a feeling of dizziness, which disappear on the person's assuming the horizontal position. Now and then appear also præcordial anxiety, fainting and threatened collapse. On the other hand, conditions of excitation, delirium, etc., are very seldom observed. Should they, for instance, occur after the hypodermic exhibition of the remedy, the fact would indicate the probable presence of

*Hager, Pharmic. Centralhalle, 1880, No 46, p. 408.

†King, Vierteljahrschr. f. Dermatol. und Syphilis, 1879, p. 370.

quinidia in the quinia. Following the hypodermic use of quinidia, Chirone and Curci observed the occurrence of epileptiform convulsions. Quinidia is much less soluble than quinine and deflects the polarized rays to the right, while quinine turns them to the left. These effects of quinine on the circulatory apparatus are observed in a lowering of the heart's action, pallor of the face and coldness of the lips and surface. These symptoms may occur singly or they may be accompanied by one of the affections which will be considered hereafter, and may last for hours or days.

The skin of many persons is affected in a peculiar manner by the internal exhibition of even small doses of quinine. The exanthems which are thus caused are distinguished by their variety. Worthy of note as bearing on the explanation of these affections is an observation first made by Chevallier,* and afterwards by other authors, that workmen in the manufacture of quinine are liable, through contact with the drug, to an affection of the skin which manifests itself in a vesicular, pustular or papular eruption on different parts of the body, as on the hands and upper and lower extremities. It follows from this fact that when affections of the skin follow the medicinal use of quinine, these are due solely to the fact that the drug is dispersed in the skin where it causes lesions, their extent being, probably, conditioned on the vascular supply. As more confirmatory of this view than the declaration of Chevallier, may be mentioned the fact, determined through experiment by H. Munk.† On moistening the electrodes with a solution of quinine in sulphuric acid and passing a current through a part of the body, the skin of this part was noticed, immediately after the interruption of the current, to be anæmic, depressed and dry. In the course of an hour after the passage of the current the skin thus acted on became so markedly swollen as to be elevated above the surrounding skin, without, however, suffering any change of color. The swelling subsided in the course of several hours, leaving in its place a hyperæmic spot which was dotted with a large number of extravasations of blood of about the size of a pin's head. These extravasations also remained

*Chevallier, Annal. d'Hygiene et de Médec. lég. 1851, T. 68, p. 5.
†Munk, Archiv. f. Anat. u. Physiolog. 1873, H. 5.

after the hyperæmia had disappeared. Quinine could still be detected in the urine twelve hours after the passage of the current. The passage of the quinine thus gave rise to an erythema which was followed by a purpura-like eruption.

A further illustration of the local origin of quinine eruption is given by Délioux de Savignac* who observed a "pruriginous eruption" after he had applied an ointment of quinia sulph. to the skin.

Analogous eruptions are also caused by the internal administration of quinine. These present themselves according to Grissac,† as :

1. Purpura.
2. Roseola.
3. Scarlatiniform exanthema.
4. Eczema.

1. The petechial form was first observed by Vépan.‡ He reports the case of a lady who took 0.1 gramme (gr. iss) and afterwards 0.15 gramme (gr. ijss) of quinine for neuralgia. Two days afterwards the entire body was covered by purpuric spots which disappeared in the course of nine days but to reappear after the administration of the drug was resumed. In this case the severity of the eruption was in proportion to the size of the dose, and during its existence there was bleeding of the gums. Gauchet§ also noticed an eruption of this nature in a lady who had previously expectorated blood after taking quinine. The petechia was profusely spread over the entire body ; it disappeared after the suspension of the drug.

2. Daubœuf** has frequently noticed a simple roseola, differing but slightly from that to be next described, in both males and females. It makes its appearance with intense pruritus, most frequently after frequent doses of the drug have been exhibited, and in one case it appeared even eight days after the taking of the last dose of the quinine. It soon spreads from its local site, the extremities and buttocks, to the entire body, and usually appears in the form of desseminated patches.

*Délioux de Savignac, Articl. Quinine, Dictionnaire Encyclopéd. de Scienc. Medical, 1874, p. 188.
†Grissac, Des éruptions Quiniques, Paris, 1876, p. 8.
‡Vépan, Gaz Medic. de Strassb. 1865.
§Gauchet, Bullet. de Therap., LXXXX. p. 373.
**Daubœuf by Grissac, L. C. p. 22.

The scarlatiniform erythema was first described by English authors. Garraway* observed it to appear simultaneously with œdema of the face. In Hemming's† case it appeared after the 0.06 gramme (gr j.) of quinine and was attended by intense itching, a feeling of oppression in the præcordial region and a coated tongue, and disappeared by slow desquamation. Skinner‡ observed its appearance in a lady after a dose of 0.06 and 0.03 gramme (gr. j—gr. ss). It was attended with shivering and rigor and spread over the whole body and disappeared only after a desquamation which lasted for three months.

We shall now consider the mixed form of the quinine exanthems—a combination of the scarlatiniform eruption and acute eczema. Köbner§ described an eruption of this nature. After the exhibition of 0.22 gramme (3½ gr.) of the sulphate of quinine the patient, a lady, was attacked with chills, præcordial anxiety, nausea, vomiting and burning heat of the skin, leading to an erroneous diagnosis of scarlatina. When the quinine was repeated the face became slightly swollen and covered with a uniform dark red which spread also over the scalp, ears, neck and extremities. A few spots of normal skin remained on the arms. The lower third of the flexor surface of both thighs was normal, but isolated papules of the size of a pea and of a dark red color were scattered over the extensor surface, the intervening surface, however, being normal and its epidermis revealing fine wrinkles. Heusinger** contributes a somewhat analogous observation. After the administration of even 0.025 gramme (½ grain) of quinine to a lady, a nodular erythema resembling erythema exsudativa multiforme, appeared on the eyelids, cheeks and a portion of the forehead, with accompanying headache, fever, nausea, an intense burning sensation, distinct œdematous swelling. At another time in the same patient a dose of 0.1 gramme (1½ gr.) of quinine only gave rise to some herpetic vesicles on the cheeks, which disappeared at once in a branny desquamation, on suspension of the drug.

*Garraway, British Med. Journal, 1869, II., p. 388.
†Hemming, Eod. loco, p. 533.
‡Skinner, Eod. loc. 1870, I. p. 103.
§Köbner, Berl. Klin. Wochenschrift, 1877, p. 305.
**Heusinger, Berl. Klin. Wochenschr. 1877, p. 361.

The papules on an erythematous surface may be changed into vesicles, and thus cause the eruption to assume a closer resemblance to eczema. In such event the itching may be absent and the general symptoms be but slightly developed. Thus Denk* noticed in a boy who had taken 0.8 gramme (12 grains) of quinine in four days, the appearance of an eruption which was unattended with itching, and which spread over the entire surface, was of a scarlatinous red color, but became pale on pressure, and was dotted throughout with numerous yellow vesicles of the size of a pinhead, distributed chiefly on the neck, in the arm-pits and over the sternum. With the exception of a slight rise in the morning and evening temperature there was no constitutional disturbance. On suspending the drug the vesicles began to break and dry up. The desquamation occurred in the form of small scales and large flakes.

The appearance of an acute eczema may, according to Grissac, be more closely simulated than in the cases just referred to, if the numerous vesicles become ruptured and thus unite to form a thick crust. There are, however, no reports of cases of this nature in German literature.

In order to arrive at a differential diagnosis of the quinine eruption and scarlatina, it is necessary, according to Köbner, to note the course of the temperature and to detect quinine in the urine. In addition one should also be on the lookout for the absence of the scarlatina tongue and of the inflammation of the palate and tonsils, the too slightly increased frequency of the pulse for the stage of scarlatinal efflorescence, and the onset of the scarlet rash without prodromata. Valuable diagnostic points are the detection of quinine in the urine, either by observing its fluorescence after the latter has been freed of its chloride of sodium (either through precipitation with nitrate of mercury) or by the separation of the quinine in the form of an iodide by means of a solution of iodine (2 parts iodine, 1 of iodide of potassium and 40 of water). The iodide of quinine is soluble by the aid of heat.

More unpleasant than any of the symptoms heretofore considered are the disturbances in the organs of special sense which have been observed to follow the exhibition of quinine.

*Denk, Wiener Med. Wochenschr, 1880, p. 946.

We shall first consider the disturbances of vision, first accurately described by A. von Graefe.* Photophobia and even transient amblyopia has been observed to follow small doses. During the continued use of larger doses, graver disturbances of function supervene which may continue for a long time and be with difficulty removed by therapeutic measures. Thus Graefe noted the case of a man, who in order to break up an intermittent fever, took quinine in increasing quantities until the dose had reached 0.9 gramme (gr. xjv.), and until the entire quantity taken had reached upwards of 30 grammes (one ounce). The dose being increased one-third daily, weakness of vision appeared in the right eye, to be followed, in a few days, by total blindness. The left eye remained sound. An ophthalmoscopic examination three months later revealed nothing abnormal, although the quantitative perception of light had failed on the right side. Holding the cause to be a disturbance of the intracranial circulation, Graefe abstracted blood from the temple by means of Heurteloup's leech. Following this there was first a gradual return of the quantitative perception of light, then a motion of the hand could be detected, and after a time there was a return to the normal condition. In another case, in which 1.8 gramme (gr. xxvij) of quinia sulphate had been taken daily in the same manner for the relief of an intermittent, and in which there was a high degree of bilateral amblyopia, the sight of the left eye was completely restored, spontaneously—but that of the right eye returned only sufficiently to permit the reading of large type.

Knapp, of New York, has recently examined cases of the untoward effects of quinine on the eye. He found the power of sight diminished in various degrees, and in exceptional cases there was amaurosis with immobility of the pupils. Where there remains a fraction of visual power, a contraction of the field of vision can always be demonstrated. The perceptions of color and light are always diminished. In well marked cases the ophthalmoscopic image has the appearance of an embolus of the retinal arteries, and the red spot in the macula lutea is wanting. The retina does not appear opaque, the papillæ are white and flat, and the vessels are highly contracted,

*Von Graefe, Arch. f. Ophthalmol. Bd. III. 2, p. 396.

in some instances so much so as to leave them scarcely discernible. The diminution in the acuteness of vision continues for some length of time. The prognosis is favorable.

In the same manner the function of the ear may be similarly affected to that of the eye, and this disturbance may occur in varying degrees of intensity, either conjointly with that of sight or independently of it. Very frequently—in about 90 per cent. of all cases—as the mildest form of the disturbance, only a buzzing or ringing in one or both ears may occur simultaneously with other nervous disturbances; difficulty of hearing and even deafness may, however, also supervene. These symptoms, according to Briquet* are in most cases but temporary. As opposed to this statement Bailly† maintains that irremediable deafness may follow the administration of quinine. The cause of these disturbances of hearing is unknown. Roosa‡ attributes the effects of quinine on the ear to congestion in the organ. In an hour after the ingestion of the drug he noticed a slight injection of the vessels of the manubrium mallei and a sensation of increased warmth in the external ear. Guder, § on the other hand, found in his experiments bearing on the same subject, that the exhibition of one gramme (gr. xv) of the muriate of quinine was followed by a reduction in the temperature of the ear, of 0.56° C. within from two to two and a quarter hours. The same dose, and in the same length of time, caused lowered perception of hearing, as tested by the watch and the ordinary tone of voice. Examination of the tympanum failed at any time to reveal hyperæmia, neither was there any such alteration in the external meatus. So far from this there was at the height of the effect of the drug, rather a lowering of the color of parts naturally red.

It is further to be noted that a gastro-intestinal catarrh of varying degrees of intensity not infrequently follows the use of quinine. For this reason Binz** calls attention to the danger in fever of giving by the stomach such salts of quinine as are not readily soluble. Quinine in a slightly acidulated solution is readily absorbed and may be given for weeks without ill effects

*Briquet, Traité Thérapeut. de Quinquina et de ses Préparat. Paris, 1853.
†Bailly, Gazette Médic. de Paris, 1850, 9.
‡Roosa, Transactions of the American Otological Society, Vol. II, part 1, 1875.
§Guder, Experimente über die Chininwirkung. Inaug. Dissert. Berlin, 1880.
**Binz, Deutsche Klinik, 1871, 46, p. 409

but when given in the form of pills or powders (and this is particularly so in the case of the slightly soluble sulphate) it is apt to cause irritation of the stomach and bowels, owing, probably, to the deficiency of the acids of the stomach in fever patients.

It was further noted by Guyochin* that slight irritation of the kidneys and of the mucous lining of the bladder and the urethra may follow the use of quinine, owing probably to the fact that the drug is carried directly to these parts. Faginoli† treated a child in whom there was pain in the urinary passages and a discharge of a few drops of blood on micturition, following each administration of quinine. Monneret observed positive hæmaturia to occur in this manner, and Piorry and Briquet have observed the occurrence of symptoms of cystitis in a very few cases, following the ingestion of quinine. More recently Rivet‡ has reported a case in which there occurred spasms of the bladder and hæmaturia as an effect of an ordinary dose of quinine.

There is mentioned in the case noted by Gauchet, as above, a symptom which is quite unique in the literature of quinine, viz., hæmoptysis. Simon de Ronchard § first noted the occurrence of several cases of hæmoptysis following the administration of quinine in doses of 0.5 gramme (gr. viij) daily. In the persons thus attacked, the lungs and heart were healthy. The hæmoptysis promptly ceased with the suspension of the drug, but when it was renewed, blood again appeared in the sputa. It has not yet been determined how this effect of quinine is induced. The investigations of Merat have, however, established the fact that quinine may be found in the bronchial mucous membrane after the internal exhibition of the drug.

The symptoms named seldom call for treatment inasmuch as they spontaneously disappear on the suspension of the drug. When the debility which has been referred to is excessive, it will be found necessary to prescribe tonics according to the symptoms. For the purpose of preventing the head symptoms which

*Guyochin, Absorption, Action Physiologique et Thérapeutique de la Quinine. Paris, 1872.

†Faginoli bei Grissac, l. c., p. 43.

‡Rivet, L'Union Medicale, Nov. 1, 1881.

§Simon de Ronchard, Gazette des hôpit, Janvier, 1861.

so frequently attend the employment of quinine, Wade* recommends bromhydric acid. Fothergill tested this drug and was able to corroborate its claims. He prescribed, diluted with water, 2—12 grammes (½—3 fluidrachms) of the acid prepared by precipitating a solution of bromide of potassium, 47 parts, water, 350 parts and tartaric acid, 58 parts. Rivet has recommended the subcutaneous administration of morphine as a remedy against the accidents following the use of quinine.

Lightfoot† observed a rapid disappearance of the quinine eruption after the taking of 25 drops of tr. hyoscyamus and alkaline baths. Heusinger (l. c.) powdered the affected portions of the skin with wheat flour.

SALICYLIC ACID—SALICYLATE OF SODIUM.

Salicylic acid, owing to its liability to be followed by unlooked for action, is to be classed with such drugs as are particularly apt to cause untoward effects. Several of the symptoms already indicated appear to be tolerably typical concomitants of the antifebrile virtues of the drug and are thus specially liable to follow its employment. To these symptoms belong several which are yet to be treated of, which are especially referable to the central nervous system.

The occurrence of other symptoms, such as changes in the skin and functional disturbances of internal organs, is quite rare and is probably due to an idiosyncrasy in the person affected. They have all, however, this feature in common that they readily disappear, leaving no trace of ill effects behind.

The internal exhibition of salicylic acid causes a repulsive taste, and a burning and grating sensation in the mouth and throat. After its absorption, we may, as noted by Bertagnini, the first experimenter into the physiological properties of this drug, and afterwards also observed by Stricker,‡ have buzzing in the ears, difficulty of hearing and profuse perspiration; these symptoms do not, however, contraindicate the further employment of the drug. Perspiration supervenes in about two-thirds of the cases, and is sometimes as profuse as that following jaborandi.

*Wade, Ref. Virchow, Hirsch, Jahresber. 1876. L. p. 400.
†Lightfoot, Brit. Med. Journal, 1870, L. p. 30.
‡Stricker, Berl, Klin. Wochenschr, 1876, No. 8.

Patients, and particularly phthisical patients, are very much troubled by it. Other authors have observed more significant disturbances of the nervous system. Thus Riegel* noticed in addition to the symptoms indicated, and following the exhibition of 4–6 grammes (1–1½ drachms), the occurrence of headache, dizziness, and transient delirium; and Schuhmacher,† in addition to these, observed visual hallucinations which caused considerable anxiety. There may further occur, according to Riess,‡ in addition to these psychical disturbances, dimness of vision and a flickering before the eyes. Knapp§ noticed diminution of the acuteness of vision and contraction of the retinal vessels of a similar nature though of a less degree, than follows the use of quinine. On the other hand Müller,‖ observed in a diabetic patient, to whom he had given 15 grammes (℥ ss) of the salicylate of sodium daily, for nine days, a condition of mental depression with severe headache and mental weakness, and, simultaneously with these, peculiar motor disturbances. The patient complained also of weakness in the legs, uncertainty of gait, a paretic inclination of the body to the right side, and notwithstanding the fact that his visual powers were intact, he ran against objects standing in his way These symptoms disappeared within five days after the suspension of the drug, but returned on a repetition of the drug in smaller doses.

Goltdammer** observed the occurrence of collapse of different degrees of intensity in several cases after small doses—5 grammes (gr. lxxv)—of the salicylate of sodium.

The manner of the occurrence of these symptoms—which bear a certain resemblance to the effects of quinine,—has not, as yet, been investigated. They are probably the expression of a direct impression of the drug upon a certain portion of the brain.

Of the functional disturbances of internal organs, those which affect the stomach and intestines first demand attention.

Goltdammer found in a post mortem of a patient suffering

*Riegel, Berl. Klin. Wochenschr. 1876, p. 182.
†Schuhmacher, Deutsche, Med. Wochenschr, 1875, No. 18.
‡Riess, Berl. Klin. Wochenschr, 1877, p. 29
§Knapp, Wien. Medic. Wochenschr. 1881, p. 1237.
‖ Müller, Berl. Klin. Wochenschr. 1877, p. 29.
**Goltdammer, Berl. Klin. Wochenschr. 1876, p. 47.

from acute miliary tuberculosis, to whom twelve grammes (ʒ iij) of salicylic acid had been given, several deep, pea-sized ulcerations on the mucous membrane of these organs. This is the only observation of this nature on record, and the condition was probably due to hæmorrhagic erosion, caused by the irritation of the drug on parts previously changed. As opposed to this is the statement of Riegel (l. c.) that he had never noticed a change in the œsophageal, gastric or intestinal mucous membrane even after doses of from 4 to 6 grammes (ʒ j to ʒ jss) of the acid. It is none the less true, however, that there have been cases reported at different times in which the employment of salicylic acid and the salicylate of sodium has been followed by pain in the stomach, vomiting and diarrhœa. Lepine noticed similar symptoms with collapse after the administration of two doses, at an interval of four hours, of 4 grammes (ʒ j) of salicylic acid. It appears as if the drug is also capable, under certain conditions, although very seldom, of causing irritation of the kidneys. Thus Lürmann* reports a case in which four grammes (ʒ j) of sodium salicylate gave rise to albuminuria, with œdema of both forearms and legs, which disappeared with the suspension of the drug and returned on its being again administered. Müller (l. c.) noticed a diminution in the secretion of urine and albuminuria after larger doses of the drug. Balz† observed, besides albuminuria, hæmaturia, as a result of the use of salicylic acid and salicylate of soda, and referred the cause directly to inflammation of the parenchyma of the kidneys.

It yet remains to consider the changes in the skin which have been observed to follow the use of the sodium salicylate, changes which occur in the form of erythema or urticaria or petechiæ, and are usually accompanied by intense itching.

In a case reported by Heinlein,‡ in which four grammes (ʒ j) of the drug had been given to a patient suffering from articular rheumatism, there supervened, with intolerable itching, a diffused redness of the left side of the face, the lower extremities and the right side of the chest, and also a slight œdema of both eyelids, the upper lips and the lower extremities as far as

*Lürmann, Berl. Klin. Wochenschr. 1876, p. 477.
†Balz Archiv. f. Heilkunde, Vol. XVIII. p. 63.
‡Heinlein, Aerztl. Intelligenzblatt, April, 1878.

the middle of the thighs. Within twenty-four hours after the drug had been withdrawn these symptoms had all disappeared. When four grammes (℥ j) of the salt was given later on, there occurred, accompanied by itching, a diffuse erythematous redness, while the whole abdomen, and also the lower extremities were covered with diffusely scattered wheals on the reddened base. The wheals disappeared spontaneously in the course of an hour, and the other symptoms on the following day. Leube, also, witnessed an urticaria occurring after a dose of four grammes (℥ j) of the salicylate of soda. Freudenberg* observed a petechial exanthem in a case of marasmus, to whom five grammes (gr. lxxv) of the sodium salicylate had been given daily for five days. The very pruritic petechiæ, some of which were as large as a fifty cent piece, first appeared on the back, from which they spread the next day over the breast, shoulders, arms, hips and thighs. In the course of eight days the spots became paler and the epidermis was thrown off in great flakes from the diseased parts. After complete recovery five grammes of salicylic acid, given in capsules, was followed by similar results. Rathery† found in his own case, that after each employment of the salicylate of soda there appeared on his hands and other parts of his body a pemphigus-like eruption. Other authors have also reported the occurrence of herpes labialis.

RESORCIN.

This more recent addition to the materia medica produces, as do also the other febrifuge drugs, when given in active doses, untoward effects, especially referable to the central nervous system. Lichtheim‡ and Brieger§ have reported facts pertaining to this point.

The effects of a dose of 2–3 grammes (gr. xxx to gr. xlv) of resorcin, given either in solution or in substance are manifest in a few minutes, the symptoms being dizziness, buzzing in the ears, and increased frequency of pulse and respiration. The face also becomes flushed and the eyes glisten, the patient being thrown into a condition simulating intoxication. Frequently

*Freudenberg, Berl. Klin. Wochenschr. 1878, p. 630.

†Rathery, Gazette des hôpit, 1881. 149

‡Lichtheim, Correspondenzblatt f. Schweiz. Aerzte, 1880, 14, 15 Juli.

§Brieger, Centralbl. f. Med. Wissenschaft, 1880, 37.

there is delirium and accompanying hallucinations. The speech becomes unsteady and slight convulsive twitchings attack the hands.

Shortly after the ingestion of the drug the surface becomes moist, and in 15 or 20 minutes there occurs a copious perspiration. With this there is a reduction of temperature and a disappearance of the symptoms of excitation referred to. Brieger noticed the onset of collapse during this latter stage, which became so great with the defervescence as to demand active stimulation.

The defervescence lasted only a short time. The fever suddenly reappeared in the course of two or three hours, preceded by a sensation of chilliness and even a decided rigor.

CHINOLINUM.

Chinoline, or the tartrate of chinoline, recently recommended as an antiseptic, but more particularly as an antipyretic, has answered to a certain degree the requirements laid on it. It is given in intermittent fever in dozen of one gramme (gr. xv) before the time of the expected paroxysm, and in the form of powder, wafers or the following solution:

℞ Chinolini, 1 gramme (gr. xv.)
Aq. destillat.
Syr. rub. idaei aa 50 grammes (℥jss.)
Aq. laurocerasi 2 grammes (℥ss.)
M.

It is also employed in whooping cough, but the untoward effects which follow its use, and which it has not yet been found possible to avoid, have militated against its more general employment.

Pure chinoline has an intensely repugnant odor and a biting, burning taste. The tartrate possesses the same properties though in a modified degree. But the effect on the stomach of both of these preparations is more disagreeable than the properties just mentioned. In the majority of cases, as Lœwy,* among others, has demonstrated, there ensues distressing oppression and severe pain in the stomach, and, in spite of all remedies which may be exhibited to prevent it, vomiting supervenes. This property would prevent its employment in cases of high fever, sep-

*L. Lœwy, Wien. Medic. Presse 1881, No. 39.

tic diseases, etc., in which there exists great irritability of the stomach, and in which the exhaustion consequent on vomiting must be avoided.

STRYCHNIA.

The administration of even medicinal doses of strychnia may, under certain circumstances, be followed by a series of symptoms which differ only in degree from those of actual strychnia poisoning. A dose of 0.005–0.01 gramme ($\frac{1}{12}$ to $\frac{1}{6}$ gr.) of strychnia may manifest itself in gastric uneasiness, redness of the eyes, formication, increased susceptibility to external impressions, heaviness of the feet and stiffness of the limbs. Associated with these symptoms there are unpleasant tension of particular groups of muscles and painful erections. Girl* noticed on several occasions after the repeated internal exhibition of strychnia, the occurrence of periodical cramp-like seizures, which for several weeks assumed a resemblance to the tertian type of intermittent fever, and finally broke up with perspiration. After their subsidence it was possible to arouse them again with strychnia.

Children are particularly susceptible to the deleterious effects of strychnia, and it is necessary to administer the drug to them with extreme caution. Cases are known in which the hypodermic administration of the drug in medicinal doses, for diphtheritic paralysis, has been followed by a series of grave and indeed fatal symptoms.

A skin affection resulting from the internal administration of strychnia has also been described. Skinner† noticed the occurrence of a scarlatiniform eruption in a woman, after a dose of 0.0004 gramme (gr. $\frac{1}{165}$), which, however, disappeared with the discontinuance of the drug.

COLUMBO ROOT.

Columbo root, which is prescribed as a simple bitter astringent, probably contains as its active principle berberin, together with the crystalline bitter substance columbin. An experiment made by Köhler‡ on himself with an infusion of 20

*Girl, Buchner's Repertorium XXXI, 2.

†Skinner, British Medical Journal. 1870. I., p. 303.

‡Köhler, Handbuch d. physiol. Therapeutik, 1876, p. 159.

grammes to 120 grammes of water admonishes to a certain degree of caution in the administration of this drug. It caused nausea, frequent vomiting, pain in the epigastrium and finally loss of consciousness, after recovery from which he remained in a condition resembling that resulting from a debauch. These symptoms had all disappeared after the lapse of twenty-four hours. With this case before us it would seem advisable, until at least a more accurate pharmacological investigation of the drug has been made, to prescribe it in smaller quantities than is now the custom. It is probable that in small doses only the effects of the bitter principle are secured, while the alkaloid berberina manifests its action in larger doses.

QUASSIA.

Quassia which is an active poison to the lower forms of insect life, when given in small doses as a stomachic gives rise to no functional disturbance. Its continued use, however, or when given in larger doses, causes in some persons digestive disturbances, gastric oppression and nausea, with efforts at vomiting. In addition to these, according to Wibmer,* there occur in children and weakly persons, after larger doses of quassia, dizziness, headache and deafness. Barbier noticed involuntary muscular contractions in an irritable woman after an aqueous infusion in quassia.

CHELIDONIUM.

Celandine, which was formerly regarded as a specific in hepatic affections, is active only when freshly gathered. The herb then contains a yellowish milky juice which is irritant and even blistering to the skin. When given internally in small doses it may excite nausea, or a desire to vomit, and vomiting or diarrhœa, and also headache. Not infrequently also after its internal use there occur papular or vesicular eruptions on different parts of the body and particularly on the face.

CREASOTE.

In the long continued use of creasote in diarrhœa there occur, according to Richardson, dryness of the mouth, a burning sensation extending from the pharynx to the stomach, a white

*Wibmer, Die Wirkungen der Arzneimittel und Gifte, München, 1842, Bd. IV. p. 380.

membraniform coating of the tongue and increased frequency of the pulse. In a few cases there occur, also, vomiting and strangury, attended by a persistent headache.

A skin affection has also been observed to follow the exhibition of creasote. M. Bernard* reports the case of a lady in whom, regardless of the form in which he administered the drug, there occurred an eruption with intense pruritus which had the characteristics of urticaria. This disappeared with the suspension of the drug and reappeared when it was renewed.

Following the external application of this substance in caries of the teeth, should it come in contact with the gums and the tongue, it is apt to cause a swelling of the latter and also a stomatitis.

When untoward effects manifest themselves in the course of the internal administration of creasote, the drug must at once be discontinued and such gastric irritation as may have been caused treated, according symptoms, with demulcent drinks. The local effects in the mouth soon disappear, either spontaneously or under antiphlogistic or astringent treatment.

OLEUM TEREBINTHINÆ.

The oil of turpentine, prepared by distillation with water from turpentine, the resinous exudate of several varieties of fir, when exhibited either internally or externally in varying doses to certain persons, produces in them a series of untoward effects which are sufficiently troublesome to forbid the repetition of the drug in such cases.

Following the local application of the drug to the sound skin there occur erythematous changes with a feeling of warmth and pruritus, and sometimes even a vesicular-like eruption of the skin, which rapidly disappear, however, after the withdrawal of the drug. In persons who have employed turpentine for a prolonged period, the skin assumes an eczematous appearance. This eczema has no specific peculiarities, never spreads beyond the seat of its original appearance and disappears with the suspension of the drug. It acts very intensely on the surface of wounds and may even give rise to extensive inflammation. The vapor of turpentine may also cause a burning and pruritic

*M Bernard, Gazette des hôpit. 1879, p. 170.

erythema, as was exemplified in a case of rheumatism, treated by turpentine vapor baths, after the manner recommeded by Chevandier.* In animals the effects of the drug on the skin are manifested in the shedding of the hair.

Schlothauer† noticed further the occurrence of profuse saliv ation and stomatitis after a single external application of turpentine for the cure of scabies. This evidence of absorption is probably due to reflex excitation of the salivary secretion, through irritation of the mucous lining of the mouth by the turpentine eliminated in the expired air, inasmuch as turpentine taken per orem may also give rise to an increased flow of saliva and reddening of the buccal mucous membrane.

The internal employment of the oil of turpentine, a well-known method of its employment in a variety of affections, as neuralgia, phosphorus poisoning, and the colic due to gallstones, occasionally gives rise to accidental symptoms which may become intensified to such a degree as to excite grave apprehension. Thus there are occasionally observed as a result of small doses, a burning in the primæ viæ, the formation of blisters in the mouth, pain in the region of the stomach, colicky diarrhœa or strangury, which usually increase until the urine becomes bloody and of the odor of violets. With this irritation of the kidneys there may be a redness of the urethral mucous membrane and also painful erections.

The repeated exhibition of medicinal doses of the oil of turpentine is not infrequently manifest on the central nervous system, evidence of which is presented in headache, dizziness, mental vacuity. Purkinje‡ who for three successive mornings took 4 grammes (℥ i) of this oil, was attacked with sleepiness and could only with great difficulty keep awake; the intellect and power of motion remained intact. The occurrence of these symptoms is explicable, in so far as Rossbach and Fleischmann § have demonstrated the action of turpentine, in its diminishing the reflex irritability of the central nervous system. Similar manifest-

*Chevandier, Revue Medico-Chirurg. 1851.

†Schlothauer, Medic. Zeitung des Vereins für Heilkunde, 25 Juni, 1851.

‡Purkinje, Ref. in Mitscherlich's Lehrb. der Arzneimittel lehre, B t. II. p. 251.

§Rossbach und Fleischmann, Pharmak. Untersuchungen aus dem Würzburger Institut, Bd. III.

ations of constitutional effects may result from an extensive external application of the oil of turpentine.

It is finally to be noted that changes in the skin may ensue on the internal exhibition of turpentine as well as a result of its external application. According to Bérenguier* there may occur after comparatively large doses, a simple, scarlatiniform, wine-colored eruption, spreading by preference over the face and the upper part of the trunk in irregular blotches. Occasionally there appear also on the reddened base a large number of small papular points, which give the surface an eczematous appearance. In rare cases the eruption is vesicular in its nature. Brochin† has reported a number of observations, in which there always occurred in certain persons, after the exhibition of turpentine, an erythematous or urticaria-like eruption; and this occurred irrespective of the mode of its administration, *i. e.*, whether it was given pure, in capsules or in solution. The following formula is recommended as one which disguises the taste ot turpentine and facilitates its administration:

℞

Olei terebinthin, 8.0 grammes (ʒ ij).
Ætheris sulph., 3.0 grammes (ʒ ¾).
Syr. flor. aurant., 30.0 grammes (ʒ i).
Aq. dest, 120.0 grammes (ʒ jv).

M

COPAIBA.

After the employment of the balsam of Copaiba (most frequently after the first day and seldom after the eighth) there suddenly occurs, only in certain persons, however, an affection of the skin, first described by Montègre, in 1817. In the majority of such cases only a roseola is at first noticed. The rose-colored, irregular spots may, however, be transformed into true papules projecting above the skin. Occasionally the eruption is papular from the beginning, which, however, according to Bazin,‡ does not present the appearance of the ordinary febrile urticaria. Gubler and Rayer have described miliary and scarlatiniform eruptions, likewise an eczema, as sometimes, though rarely, following the employment of copaiba. The cutaneous change appears by

*Bérenguier, Des éruptions provoqueés par l'ingestion des médicaments. Paris, 1874.
†Brochin, Gaz. des hôpit., 1879, Fevr., p. 99.
‡Bazin, Leçons sur les affections cutanées artific. Paris, 1862, p. 184.

preference on the upper and lower extremities, and particularly on the backs of the hands, the knees, around the malleoli, and on the breast, but spreading eventually over the entire body, and is attended with considerable fever. According to Bérenguier* the roseola induced by copaiba resembles a papular syphilide, differing, however, from the latter in its sudden onset, the itching, its predilection for the parts of the body indicated, and a peculiar, unpleasant smell of the skin, and particularly through its disappearance on suspension of the drug.

The eruption is attended by intense itching. The spots or papules are either isolated or in groups. In the latter case they may form patches of considerable extent. The spots disappear on pressure and reappear on its removal. Should the drug be suspended on the appearance of the eruption, the latter may disappear without desquamation in a day or two, although owing to individuality on the part of the patient or a long continuance of the drug, from one to three weeks may be necessary for its disappearance. Under the long-continued use of the balsam the eruption may assume a severer form and the deeper tissues may even be involved.

In referring to a statement of Hardy,† who observed a pemphigus-like eruption after the employment of copaiba, Hebra‡ calls attention to the probable fact that in this case it was not pemphigus but urticaria, and that the wheals (quaddeln) of the latter are serous infiltrations of the epidermis which require but to be somewhat aggravated in order to be blisters.

The balsam of copaiba when employed for a long time and not necessarily in large doses, affects the various mucous membranes injuriously. It not infrequently causes loss of appetite, gastric oppression, nausea and vomiting, and still further, according to Bazin (l. c.) congestion of the conjunctiva and pharynx, and irritation of the kidneys and bladder, to the extent of even causing nephritis and cystitis.

The manner in which these effects are produced is clear. Balsam of copaiba, like other resinous substances, causes irritation of various degrees of severity, of the mucous membranes,

*Bérenguier, l. c., p. 22.
†Hardy, Gazette des hôpiteaux, 1869.
‡Hebra, Hautkrankheiten, 1., p. 673.

perhaps through the oil of copaiba or copaibic acid which it contains. Its elimination is effected through the lungs and kidneys, and thus the urinary passages may suffer irritation in proportion to the quantity of the balsam which passes through them. But the balsam may also be excreted through the skin, and thus either it itself or the glands which it contains may be the starting point of an inflammatory action. It has not yet been determined to what extent deviations from the normal vascular distribution or a peculiarity in the glandular elements of the skin are responsible for the effects noted. The fact, however, remains that after the employment of the balsam of copaiba, a peculiar odor, due perhaps to the volatile products of decomposition of the drug, is given off, and that in these cases the effectiveness of the balsam in gonorrhœa is slight.

It is to be remarked that the urine which is voided after the exhibition of copaiba, gives a precipitate with nitric acid which consists of copaibic acid, and may be easily mistaken for albumen.

Maestri and Pidoux* report that large doses of the balsam of copaiba occasionally give rise to symptoms of poisoning, among which are paralysis, with tetanoid manifestations. In milder cases there is weakness of the arms and muscles of the face and lowering of general sensibility.

CUBEBÆ (EXT. CUBEBARUM.)

The employment of cubebs is not, as a rule, attended by untoward effects. In some persons, however, it may cause colicky pains and diarrhœa.

An eruption is commonly observed only after large doses and in the case of very young persons. It then manifests itself either as an erythema or, more frequently, as a papular eruption, which, as in a case reported by Berenguier (l. c.), is diffused over the face, trunk and upper extremities, and which was also abundantly discernible on the lower extremities. The papules are miliary, but unite in many places to form larger elevations on the skin. The eruption occurs without accompanying

*Maestri u. Pidoux, Ref. Schmidt's Jahrbücher, Bd 97, p. 301.

febrile symptoms or other evidence of disturbance, and disappears in the form of bran-like scales in a few days after the suspension of the drug.

AQUA CALCIS.

The continued use of limewater through the continued neutralization of the acids of the stomach which attends it, not infrequently gives rise to disturbances of digestion and loss of appetite; vomiting has also been observed to follow such employment of it. There is increase in the urinary secretion during its use, the stools are usually retarded, and in rare cases here is diarrhœa.

To obviate these ill effects it has been proposed to substitute saccharated lime in doses of 0.5 to 1.0 gramme (gr. viij to xv) in watery solution for the lime water.

What is true of lime water in this connection is equally applicable to the carbonate of lime.

SODII NITRAS.

Löffler* noticed several changes in persons who had taken saltpetre for a length of time, by way of experiment, even though the doses did not exceed the medicinal size. On two occasions there was pain in the intestines and borborygmi. The digestion was generally not disturbed by the drug; but, varying with the quantity of the saltpetre taken, there ensued a feeling of general debility which was manifest on exertion and continued for several days after the drug had been discontinued; disinclination for either bodily or mental action, depression of spirits, fatigue on the slighest exertion, pains in the muscles and joints, particularly in the knees, and a persistent inclination to sleep.

The quantity of urea increases for the first few days following the administration of the drug; it then returns to and even falls below the normal quantity.

*Löffler bei Barth, Toxicologische Untersuchungen des Chilisalpeters, Bonn, 1879, p. 5.

ASTRINGENTS.

ALUMEN.

Following the frequent administration of alum there appear in some persons gastric disturbances, as loss of appetite, nausea, inclination to vomit and diarrhœa. This effect is due to a direct irritation by the drug, of the mucous lining of the gastro-intestinal tract, and is dependent on the degree of fullness of the stomach. For should the alum ingested not find a sufficient quantity of albumen or albuminoid substances in the stomach to precipitate it, the mucous membrane of this organ is, in a greater or lesser degree, affected by the drug. The observation of Béginaud, also of Barbier, viz., that the continued use of small doses of alum is prone to induce a cough in persons with sensitive bronchi, is also noteworthy.

BISMUTHI SUBNITRAS.

(MAGISTERIUM BISMUTH.)

There is scarcely any other drug, the opinions regarding the deleterious or the innocuous nature of which are so conflicting as are those entertained on the nitrate of the oxide of bismuth. While Monneret,* among others, asserts that the irritating or even poisonous properties which are attributed to this substance are but imaginary, that it may be administered to patients in quantities of from 3 to 6 teaspoonfuls daily without inconvenience, and that it can be beneficial only in such doses, there are many competent observers who aver that the subnitrate of bismuth in doses of from two to four grammes (℥ ss to ℥ i) may sometimes be attended with baneful untoward

*Monneret, Central Zeitung, 1849, 43.

effects. The attempt has been made to reconcile these contradictions by holding the impurities of the preparation given, and particularly the lead and arsenic which it is said to contain, responsible for these untoward effects. As a matter of fact Carnot,* among others, found lead in all the preparations of the subnitrate of bismuth which he examined, in quantities varying from one to ten per cent. Riche,† on the other hand, attributes much less importance to this and maintains that the quantities of lead which he has demonstrated to be present are too insignificant to work any disturbance in the system. Bouchut‡ would not even have the lead which is contained in the subnitrate of bismuth eliminated, holding, as he does, that it is through this substance that the preparation exerts its curative action in diarrhœa.

The proportion of arsenic in subnitrate of bismuth is also too small to give rise to the symptoms which are hereafter to be mentioned.

It then remains but to attribute the ill effects of the bismuth either to such a temporary condition of the patient as causes an abnormal reaction, or to an improper employment of the drug.

The condition of the individual may have an influence in so far as the presence of undue quantities of acid in the stomach may favor the conversion of the basic subnitrate of bismuth into a corrosive neutral salt; or, if this should be decomposed by water the acid salt may be formed in great quantities. These neutral and acid salts are, as Orfila§ demonstrated by his experiments on animals, intense poisons, setting up gastro-enteritis. The same effects would naturally ensue if the basic salt were given simultaneously with acid remedies, or if the patient should take acids after the drug. A readily soluble nitrate of bismuth would thus be formed in the stomach and would be absorbed.

The untoward effects which are observed to follow the subnitrate of bismuth, are chiefly referable to the stomach and

*Carnot, Comptes Rend. des sciences de l'Acadamie des sciences. T. LXXXVI., p. 718, 1878.

†Riche, Journ. de Pharm. et Chimie, 1878, 28, p. 147.

‡Bouchut, Jahresbuch über Pharmakog. u. Toxikol. von Dragendorff, 1879, p. 268.

§Orfila, Toxicologie übers. v. Krupp, 1854, II, p. 9.

intestines, and are nearly identical with the pathological symptoms which it is the typical action of the acid salt to excite. Thus Odier* noticed nausea after its use, and Werneck† vomiting, colicky pains, and in several cases diarrhœa, while in others there occurred obstinate constipation. With these local symptoms there were associated a sensation of heat, headache, dizziness and general debility. Not infrequently after the exhibition of magisterium bismuth there is observed a peculiar discoloration of the tongue. According to T. Lawrence Hamilton,‡ this is due to a change of the bismuth salt through the sugar formed by the action of the saliva on the starchy food. It is also possible that sulphuretted hydrogen is developed from carious teeth, and that the union of this with the bismuth gives rise to a black or greyish-black sulphuret of bismuth. It is further to be especially noted that the fæces after the employment of the subnitrate of bismuth, mostly assume a grayish-black color, and are nearly odorless. It is inferred from this that the bismuth salt is changed in the intestines, in the presence of sulphuretted hydrogen gas, into the sulphide of bismuth, and the gas is thus held fast in combination. The therapeutic indications in the untoward effects named, are a discontinuance of the drug, and the employment, now and then, of calcined magnesia in small doses, or of milk in an emulsion, etc.

ACIDUM BORACICUM.

According to the investigations of Binswanger§ boracic acid in medicinal doses is without effect on the human system; should, however, the quantity given be increased to 2 or 4 grammes (30 or 60 grains) it may cause a frequent desire to micturate and an increased flow of urine.

After 8 grammes (ʒ ij) of boracic acid, taken by Binswanger in two doses within an hour, there occurred nausea and vomiting, a feeling of pressure and fullness of the stomach, which continued for several hours.

*Odier, Journ. de Medecin. 1768, T. 68, p. 49.

†Werneck bei Wibmer, Wirkungen d. Arzneimittel, T. I. p. 418.

‡T. Lawrence Hamilton, British Medical Journal, February, 1881.

§Binswanger, Pharmakolog. Wirkungen dei Borsäure und des Borax, München. 1847.

Following the external employment of boracic acid as an antiseptic. Molodenkow* has recently reported deleterious untoward and even fatal results. A young woman who suffered from pleurisy and hydrothorax was subjected to thoracentesis without previous chloroformization. The pleural cavity was afterwards washed out with a five per cent. solution of boracic acid, following which distressing vomiting and weakness of the pulse set in. On the following day an erythema appeared on the face and soon extended over the trunk. On the third day the erythema having also spread over the lower extremities, the vomiting having ceased and the mind remaining clear, the patient suddenly died.

In a second case, after the washing out of a deep abscess in the nates of a young man, of sixteen years of age, there occurred in half an hour vomiting, debility, and a small, scarcely perceptible pulse, and in two days an erythema, first appearing on the face, hiccough and death. The autopsy revealed no cause of the death, which seems to have been due to paralysis of the heart.

The decided poisonous action of boracic acid in these cases is, perhaps, explained by the experiments of Binswanger, who showed that in the internal exhibition of this drug it is rapidly eliminated by the kidneys, while after its injection into cavities it is less readily absorbed, remains longer in the system and thus exerts its fullest action.

ARGENTI NITRAS.

The changes induced by the continued use of silver, either internally or externally, consist of a discoloration of the tissues, due to a deposit in them of the metal. As a result of this accumulation of this foreign substance we may have functional disturbances in the various organs.

The tissue changes have frequently been made the subject of microscopic investigation. Thus Virchow† examined a piece of the conjunctiva of a man for whose eye the application of a solution of nitrate of silver had been prescribed, but who, through misunderstanding, continued its employment

*Molodenkow. St. Petersburger Medic. Wochenschrift, No. 42, 1881.

†Virchow, Cellular-Pathologie, 1871, p. 250.

for four months. It had become stained to an intensely blue, nearly black color. A deposit of the silver in the tissue had occurred, "so that the superficial layers of the connective tissue were of a light yellowish-brown color, and a deposit was found in the deep, though in only the fine elastic fibres or corpuscles of this tissue. The basis or intercellular substance remained unaffected.

That the skin, even when perfectly intact, may afford ingress to the silver is illustrated by a case, reported by Gamberini,* of a woman who, in order to dye her hair black, had every two weeks, for two and a half years, applied a pomade containing nitrate of silver. There occurred dyspnœa, palpitation, ascites and œdema of the inferior extremities, on the disappearance of which the skin assumed a slate-gray to a light-brown color. In addition to palpitation of the heart, irregularity of the pulse has been observed after small doses—0.005 grammes (gr. $\frac{1}{14}$) of the nitrate of silver.

The recommendation of the nitrate of silver in epilepsy, tabes dorsalis and similar affections, has through the chronicity of these affections, and the long continued use of the drug, frequently led to the deposit of silver in the tissues, a condition and its consequences to which the name argyria has been given. The smallest aggregate quantity following which this condition has been noticed, is 30 grammes (℥ i). The discoloration may attack the entire cutaneous covering, equally, or it may be most intense at particular parts, as the face. Cicatrices, the nails and hair may likewise suffer changes of color.

Functional disturbances generally present themselves in the form of gastritis, although in many cases they are entirely absent.

As a consequence of the irritation which the drug excites upon the buccal mucous membrane, a stomatitis without salivation may occur, as observed in a case reported by Guipon.† The gums in this case were swollen and of a dark-red color, and presented a violet line on the edges. The incisor teeth were of a slate color, and the mucous lining of the mouth was exceedingly sensitive, particularly to heat.

This affection has more recently been observed by Magitot,‡

*Gamberini, Journal de Médecine de Bruxelles, Decembre, 1860.

†Guipon, Bullet. de Thérapeutique, 1866, Vol. 71, p. 86.

‡Magitot, Gazette des Hôpitaux, 1879, p. 165.

who has described it as "gingivite argentique." In this connection he calls attention to the fact that Charcot observed a papular eruption as a result of the continued internal employment of silver, and holds that both affections are due to the local irritative action of the silver.

Individual organs manifest, as a result of argyria, the following changes:

Neumann* found on examining the skin, that the silver was deposited most abundantly in the papillary layer. A few granules were likewise found in the other layers of the skin, more thickly disposed in the external wall of the hair follicles and sebaceous glands, and in the walls of the sudoriparous follicles. The epithelium—reti Malpighi—and the covering of the root sheaths (wurzelscheiden) contained none.

In the case of a man who had taken nitrate of silver in large doses for epilepsy, Frommann† found at the autopsy an ulcer between the pyloric and cardiac openings. The duodenum and jejunum were studded with numerous small black bodies, which were crowded most closely together along the sulci of the folds, presenting the appearance of dark, striped pigmentation of the mucous membrane. In the duodenum they took the form of round spots of the size of a cent piece, which were darkest at the centre and becoming lighter towards their margins. The intestinal villi (darmzotten), contained groups of small deep black bodies which were readily soluble in cyanide of potassium.

In the case of a tabetic patient, who in a single year had taken 5,672 pills, containing in the aggregate 34.032 grammes (℥ jx) of nitrate of silver, Riemer‡ found the capsules of the kidneys gray with numerous dark spots, resembling the Malpighian bodies, and the mucous lining of the pelvis of the kidneys of a grayish-blue in spots. The changes in the parenchyma of the kidneys in argyria, are described by Virchow (l. c.), after the appearance, as he found them in a preparation, in a collection in the Pathological Institute at Berlin. In this specimen there appears in the Malpighian bodies, where the

*Neumann, Sitzungsberichte d. Gesellschaft Wiener Aerzte, 1. März, 1878.
†Frommann, Virchow's Archiv., Bd. XVII.
‡Riemer, Archiv. d. Heilkunde, 1875, XVI., p. 296 u. 385.

transudation of the fluid takes place, a blackish-blue discoloration of the entire walls of the vessels, which are contracted at this point, and a similar though less pronounced discoloration in the connective tissue between the canaliculi. Thus in the whole kidney, with the exception of the parts which are particularly the seat at which eliminination is effected, only those portions are implicated which correspond to the ultimate capillary distribution in the pyramidal substance.

In addition to portions of the body indicated, Riemer and others have discovered silver in many other and widely different organs, as the meningeal membranes, the liver, the mesentery, the walls of bloodvessels, the heart, etc.

Regarding the manner of the absorption and deposit of the metal, opinions differ. Riemer maintains that the pigment as such, is, in the form of reduced silver, absorbed by the walls of the intestines, where it is first stored up, soon however to be carried further by the lymphatics, being partially deposited on the way, but the greater portion being carried into the current of the circulation. It finds its way thence through the walls of the blood vessels, in which a portion of it is deposited, and is finally permanently stored up in the tissues. Riemer thus regards the cause of argyria as purely physical, after the same manner as in anthracosis pulmonum and in the tatooing of the skin. He is supported in this view by the later experiments of Huet,* who induced the passage of particles of silver into the tissues by a sort of diapedesis. In this, however, he differs from Frommann, Delioux and others, who hold that it is only possible for the soluble salts of silver to be taken up from the intestinal canal, and that, therefore, argyria occurs through chemical process, a precipitate taking place in the parts attacked.

In the differential diagnosis of argyria and Addison's disease, the following points indicated by Gamberini are noteworthy: In the "bronze sickness the color varies between a brown and a black, while in argyria it is of slate-gray, with a tinge of red. On washing the skin in argyria with a solution of iodine there is a marked change in the color, which change does not occur in the case of the discoloration in Addison's disease."

*Huet, Journal de l'Anatomie, 1873, p. 108.

The treatment of argyria may have reference both to the gastric symptoms and to the discoloration of the skin. In regard to the former, existing signs of intestinal irritation must be treated symptomatically. With a view to bringing about a clearing up of the color of the skin, the internal use of the iodide of sodium or the iodide of potassium, so successful in the hands of Gamberini, and the long continued employment of warm baths should be tried. As a prophylactic measure it is necessary to exercise great care that the silver be not employed for longer than three months, and that the aggregate amount administered do not exceed 15 grammes (3 jv.)

PLUMBI ACETAS.

When the acknowledged poisonous nature of the acetate of lead, in common with that of the other combinations of this metal, and the extensive exhibition of the same, both internally and externally, in relatively large doses, are taken into consideration, it is singular that deleterious untoward effects are not more frequently observed than is actually the case. The fact must, however, be noted that in those cases of saturnism, which follow the employment of lead in the arts or are due to its presence in the food, the introduction of the metal has generally been going on for a much longer time than is devoted to its most prolonged exhibition for therapeutic purposes, and that the majority of the functional disturbances in lead poisoning are excited by the extremely gradual deposit of the minutest particles of lead in the organs, and its later cumulative action. That there are exceptions to this mode of the occurrence of lead poisoning is illustrated by the fact particularly insisted on by Romberg,* that certain persons who have been long subjected to the action of lead have escaped its effects, while others are quickly brought under its influence.

Wibmer† collected a few cases in which, probably through causes peculiar to the individual, such as defective elimination through the intestines, kidneys, etc., deleterious untoward effects

*Romberg, Lehrbuch der Nervenkrankheiten, I., p. 167.
†Wibmer, l. c. Bd. IV. p. 23.

were observed to follow the exhibition of even medicinal doses of the acetate of lead. Baker* noticed loss of appetite, pain in the stomach, constipation and paralysis of three weeks' duration; one hand, in a man who had for four days, morning and evening, taken 0.06 gramme (gr. j) of the acetate of lead for the relief of hæmaturia. In another case colicky attacks, which continued during several months, followed the daily exhibition, for but three days, of 0.24 grammes (gr. jv) of the drug. Tanquerel des Planches,† who first thoroughly studied and carefully described the action of lead, cautions against the too free internal exhibition of its preparations, as being very prone to give rise to undesirable symptoms.

The external application of lead in solutions and ointments is also said to have developed unpleasant effects. We shall first note those cases in which discoloration of the skin, of longer or shorter duration, is reported to have followed the employment of the preparations of lead. Thus Foucaud de l'Espagne‡ cites the case of a woman who, under the instructions of a physician, employed as an astringent collyrium, a solution of the acetate of lead. Another physician having at the same time ordered her to take sulphur baths for the relief of rheumatism, there occurred a black discoloration of the eyelids, which spread over the cheek bones and was only removed after six days by washes of infusions of aromatic herbs. Bérenger-Feraud § contributes a similar observation. In this case the discoloration disappeared only after a duration of thirty months, in spite of all conceivable acid, alkaline and aicoholic washes and cosmetics.

The application of solutions of lead to the mucous membrane and abrasions, appears but rarely to excite symptoms of lead poisoning. Tanquerel des Planches noticed such a case attending the application of lead-water compresses to the eye. Percival‖ noted the appearance of gastric pains after the repeated application of compresses wet with a solution of ace-

*Baker, Lond. Med. Transactions, I. and II.

†Tanquerel des Planches, Traité des Maladies de plomb, übers. von Frankenberg II., p. 343.

‡Foucaud de l'Espagne, Gazette des hôpit, 1863, No. 153, p. 611.

§Bérenger-Feraud, Gazette des hôpit, 1864, p. 62.

‖Percival, "On the Poison of Lead," 1774, bei Wibmer, Bd. VI., p. 237.

tate of lead to a contused shoulder, the pains disappearing with the suspension of the application and reappearing with its renewal. The washing of a large ulcer of the leg with lead-water, and the application of a lead plaster also after four days caused a colic, and paralysis of the extremities, which soon disappeared on the discontinuance of the drug. In another case, noticed by Werdmann, a sweetish styptic taste in the mouth and a stiffness of the neck followed the application of lead-water to an ulcer. In this case also the symptoms recurred and disappeared with the exhibition and suspension of the drug.

There is, from a physiological point of view, no room to doubt the possibility of the occurrence of these effects of lead. Inasmuch as it is an established fact, that under certain circumstances lead may be taken into the system through the sound skin, the penetration of the combinations of lead, and particularly the caustic preparations which throw down precipitates with albumen, is intelligible. It is true the quantities thus absorbed are very small, but still they are sufficient to give rise after a few applications, to the appearance of the drug in the urine. Why it is that injurious effects so seldom ensue on the application of the drug in this manner is not known. Similar individual conditions, however, obtain in the case of the majority of drugs, and they are independent of the manner of their absorption.

ZINCI OXIDUM.

The oxide of zinc, in common with all the other combinations of the metal, the sulphate alone excepted, which have during the past few decades been exhibited in affections of the central nervous system, as epilepsy, eclampsia chorea, not infrequently, like the other metallic salts, manifest undesirable untoward effects, referable mostly to the digestive tract. The doses following which the effects may present themselves may be as small as 0.2 to 0.3 gramme (gr. iij to gr. v). In many persons the symptoms are nausea, disgust, and gastric oppression varying in degree with the individuality of the person and the quantity of food in the stomach, for the irritation of the

gastric mucous membrane is intensified in proportion to the opportunity afforded the zinc salts, either directly or after their solution in the stomach, to form an albuminate on the mucous membrane. Should there be sufficient food present to form an albuminate with all the zinc given, the irritative property of the zinc is almost negatived, inasmuch as the zinc albuminate goes through the regular process of digestion and is taken up into the vascular channels.

The continued use of small doses of the salts of zinc is to be guarded against, since they are liable, even with the greatest care, to produce ill effects on the different functions. Thus Werneck* found the repeated use of 0.2 gramme (gr. iij) doses of the zinc oxide to produce in his own person, gastric oppression, eructations, slight confusion of thought and later, dizziness and a feeling of bodily exhaustion, and following the fourth dose severe thirst, gastralgia, slight vomiting and a sensation of tension in the limbs. Should the zinc salt reach the intestines, where it may irritate the mucous membrane, diarrhœa is superadded to the above symptoms. Analogous symptoms have been noted by other authors to follow small and long continued doses. It yet remains to be noted that, according to Pareira, the frequent use of medicinal doses of the zinc salts may induce a zinc dycrasia, similar to chronic saturnism, which is characterized by obstinate constipation, emaciation and anæmia.

The symptoms above indicated may certainly be very frequently guarded against by administering the zinc salt in soluble form, the lactate, for instance, and upon a full stomach. Should the untoward effects have supervened, milk and the white of eggs may be given, in order that the zinc which may be present may form combinations with them. But special effort must also be made by means of laxatives and diuretics to secure the speedy elimination of the drug from the body.

CADMII SULPHAS.

The sulphate of cadmium was employed by Grimaud† as

*Werneck, Medic. Chirurg. Zeitung 1831, III., p. 317; ref. bei Wibmer l. c. Bd. V., p. 469.

†Grimaud, Gazette Médical de Paris, 1851.

an internal remedy in syphilis, chronic rheumatism, etc. It irritates to a much higher degree than the zinc salts, the stomach and the intestinal canal, such irritation being, however, only of a transitory nature. Burdach observed after 0.06 gramme (grj) salivation, colic, and hypercatharsis with tenesmus.

An ointment of the cadmium sulphate produced, according to Grimaud, a pustular eruption similar to that caused by tartar emetic.

BARII CHLORIDUM.

The chloride of barium which was formerly, on the recommendation of Hufeland,* regarded as a specific in the various forms of scrofula, causes sometimes in certain persons and in quantities not exceeding the maximum dose (0.12 [grij], the amount daily ingested not exceeding 1.5 gramme [grxxij]), functional disturbances in organs of the most diverse character. According to Lisfranc,† the poisonous action of the barium chloride varies with the climate, inhabitants of southern latitudes tolerating decidedly larger doses than those living at the north.

The disturbance of the stomach and bowels are manifested in the nausea, and even vomiting, loss of appetite, colicky pains, oppression in the epigastrium and diarrhœa. Catarrhal irritation of the conjunctiva, the nasal and respiratory mucous membrane—the latter perhaps extending from the pharynx—has, in a few instances, been observed to follow the employment of baryta.

The prolonged use of medicinal doses may, as Hufeland has observed, intensify the effects already detailed until symptoms of well-marked gastro-enteritis may supervene, and in addition to this symptoms referable to the central nervous system, as dizziness, great anxiety, faintness, muscular weakness, trembling and even convulsions. Kohl‡ observed in one case in which the barium chloride had been administered for twenty four days, salivation, swelling of the salivary glands, a foul odor of the breath and loosening of the teeth.

It is not improbable that this aggravation of the symptoms

*Hufeland, Ueber die Natur, Kenntniss und Heilart der Scrofelkrankheit, Berlin, 1819.
†Lisfranc bei Bernatzik, Encyclopædie der ges. Heilkunde, 1880, Bd. II., p. 15.
‡Kohl bei Husemann, Toxicologie, p. 945.

by the prolonged use of baryta is due to a cumulative action of the drug, in consequence of its tardy elimination by the urine and fæces. This view is supported by the fact that a demonstrable quantity of the barium chloride is transformed in the body into the sulphate, which latter being a substance which is dissolved with difficulty, is deposited at the place at which the change is effected, whence it is slowly eliminated from the system. In this manner it is possible for an intense activity of the baryta to manifest itself, and one which may continue for a long time after the administration of the drug has been suspended.

These facts explained an observation of Schwilgué,* who found that when he gave minute doses of baryta, the irritation of the various organs was aggravated after the suspension of the drug, and continued for at least seven weeks thereafter.

The treatment of the symptoms mentioned consists in the first place in the suspension of the drug. The gastric symptoms demand such agents as are calculated to allay the inflammation. With a view to facilitating the elimination of the baryta diuretics are to be recommended. The employment of a direct antidote, such as the sulphate of sodium or magnesium is indicated in only very severe cases.

ACIDUM TANNICUM.

The susceptibility to the action of tannic acid varies with the individual. Thus Tully, who for a week took 0.6 grammes (gr. x) of tannin daily, experienced nothing further than slight nausea and anorexia, while Hennig,† after taking but 0.2 grammes (gr. iij), experienced pain in the stomach and bowels, a coated tongue, eructation, thirst, tenesmus and an aggravation of a habitual hæmorrhoidal congestion.

Roller‡ observed after a large dose of tannin, taken for the relief of a diarrhœa, pain in the stomach and abdomen, violent emesis and a constipation which continued for fourteen days with slight fever. After the constipation was relived the

*Schwilgué, Matière Mèdicale, T. I., p. 409.
†Hennig, Archiv. f. physiol. Heilkunde, Bd. XII., 1853.
‡Roller, Wiener Medic. Wochenschrift, 1865, 97.

stools were for a time mixed with blood and pus. This was probably due to a caustic action of the tannin on the gastric intestinal nerve.

In order to guard against such symptoms with a certainty, and to permit of the prolonged employment of tannin, L. Lewin* recommends the administration of either the albuminate of tannin or an alkaline solution of tannin. The first is readily prepared by dissolving the quantity of tannin ordered in a little water, precipitating it with a solution of albumen, and then adding an excess of albumen until the albuminate thus formed is dissolved. For a solution of 2 grammes (gr. xxx) of tannin in 100 (℥ iij) grammes of water, the white of one egg dissolved in 100 ccm (℥ iij) of water, and then filtered, is sufficient. The alkaline solution of tannin may be prepared by adding to the solution of the desired quantity of tannin in water, carbonate of sodium, until the reaction becomes feebly alkaline, or by the addition of albumen to it, and by adding the carbonate of sodium until the abuminate of tannin again dissolves. These solutions may be given as follows:

(1). *Tannin albuminate:*

℞ Solut. acid. tannic, 2 %, 100 grammes (℥ iij).
Adde agitando.
Sol. Albumin. ovi 100 grammes (℥ iij).
M

This solution has a milky appearance, a very slightly astringent taste and is well borne by even small children. Should more tannin than 2:100 be desired, the proportion of albumen must also be increased.

(2). *Tannate of Soda:*

℞ Solut. acid. tannic 1.0—5.0 grammes (gr. xv to gr. lxxv) to 150.0 grammes (℥ v).
Adde solut. sodii bicarb. q. s., ad react. alkalin.
M

In this formula the tannin is most readily absorbed. This very slightly alkaline solution must be kept in a well stoppered bottle and employed in from one to two days, inasmuch as it is changed under the influence of air and light, into a light-brown, greenish-brown or dark-green color, by the products of oxidation which are formed in it.

*L. Lewin, Untersuchungen über Wirkung und Verhalten des Tannins im Thier körper Virchow's Archiv, Bd. 81, 1880.

Alkaline tannin albuminate:

℞ Acid. tannic 2.0—5.0 grammes (ʒ ss to ʒ j¼).
Aq. dest. 100.0 grammes (ʒ iij).
Adde agitando.
Album. ovi unus.
Sodii bicarb. solut. q. s. et fiat solutio limpida.
M

This solution unites in itself the tannin albuminate and the tannate of sodium. It is best adapted to cases requiring the prolonged employment of tannin. It must be freshly prepared as it does not keep for more than two days.

ERGOTINUM.

The extractum secale cornuti of Wiggers, as does also that of Boujeau, produces, now and then, in medicinal doses—0.2 to 0.4 gramme (gr. iij to gr. vj)—sickening taste, irritation of the throat, increased secretion of saliva, nausea, burning in the stomach, abdominal pains, eructations, vomiting and diarrhœa. Associated with certain of these symptoms we may have confusion of thought, head ache or sensations of chilliness, dizziness, dilatation of the pupils and also general debility, uncertainty of gait and irregularity of the pulse. Apart from the idiosyncrasy of the patient, the differences in the action of this drug are probably traceable to the variability in the chemical constitution of the preparations employed.

Following the hypodermic employment of ergotin, first recommended by von Langenbeck* (after the following formula: Ext. sec. corn. Boujeau 2.5 gramme [gr. lx], spts vini et glycerinæ 7.5 [ʒ ij]), a series of undesirable untoward effects were observed. Von Langenbeck noticed after an injection of 0.3 gramme (gr. v.) a glimmering before the eyes and pain in the shoulder. Eulenburg† noticed dizziness and vomiting under similiar conditions.

The general symptoms were more threatening in a case reported by Rezek,‡ in which 0.04 gramme (gr. ⅔) of ergotin had been injected. Five minutes after this injection the patient was seized with several general convulsions, the pupils became

*Langenbeck, Berl. Klin, Wochenschr, 1869, p. 117.
†Eulenburg, Die hypodermat. Injection der Arzneimittel, Berlin, 1875, p. 240.
‡Rezek, ref. bei. Eulenburg, l. c., p. 244.

dilated, the eyeballs rolled, loss of consciousness supervened, the skin became cool and the pulse disappeared. These symptoms subsided under cold douches and the internal administration of ether. Phillipi noticed yawning, labored breathing, dilatation of the pupils, smallness of the pulse, efforts at vomiting and incoherent speech, in a lady to whom hypodermic injections of 0.3 grammes (gr. v) doses of dialyzed ergotin were administered for menorrhagia, the symptoms supervening in from 30 to 40 minutes after each injection. This condition lasted for one or two hours and was relieved by counter-irritation and the exhibition of analeptics. It was a peculiar fact that the exhibition of ergotin to this lady in the form of pills or suppositories, caused no such untoward effects.

Hildebrandt* observed symptoms which were milder. Following six injections in the case of a female, the patient became dizzy and unsteady of gait; spasmodic contractions of the flexors of the upper and the lower extremities, nausea and constriction of the chest also occurred. The symptoms disappeared with the suspension of the drug to return with its resumption.

Of more frequent occurrence than these general systemic disturbances are the symptoms, of greater or lesser intensity of localized reaction. This is most marked after each hypodermic injection at the point of penetration, around which there occurs a painful nodular infiltration which does not go on to suppuration. Hildebrandt,* who employed the plan of injecting ergotin for the relief of fibro-myoma of the uterus, believed that the pain which thus ensues is due to the presence of alcohol in von Langenbeck's solution, which is employed. He employed, on account of this a solution of ext. secale cornut. aq. 3.0 grammes (gr. xlv) to glycerine and water, of each 7.5 grammes (ʒ ij), following which he observed less pain, although there also remained persistent nodules of the skin, which were somewhat sensitive.

Bengelsdorff† saw also as a result of injections of ergotin, after Hildebrandt's formula—the ergotin in which is not fully dissolved but remains principally in suspension—a fre-

*Hildebrandt, Berl. Klin. Wochenschr., 1872, p. 298.
†Bengelsdorff, Berl. Klin. Wochenschrift, 1874, p. 21.

quently decidedly painful and not infrequently positively phlegmonous, non-suppurating inflammation, encircling to a greater or less circumference the point of injection. Accompanying this there was usually a hard, nodular swelling, varying in size with the size of the injection, which frequently remained for eight days and over. The nodules could not be prevented either by deep insertion of the cannula or by friction.

FOLIA SALVIÆ.

The popular domestic remedy, sage leaves, occasionally employed internally in the form of an infusion, as an astringent, may under certain circumstances, as Pidoux realized in his own experience, give rise to unpleasant symptoms. This observer experienced, after taking a cold infusion, a profuse perspiration, which continued for several hours, a bitter taste, a dryness of the mouth and throat, constipation and increased frequency of the pulse. These symptoms show the effect to be due to a joint action of the tannin and ethereal oil contained in the plant.

PIX LIQUIDA.

Tar, which, in the form of tar-water, was formerly extensively administered as an internal remedy in skin diseases, and also in bronchial affections, is now most frequently employed externally, either in its pure state as an embrocation in eczema, or, in the form of tar-water, as an inhalation. In either form it may, should any very considerable quantity of its active principles be absorbed, give rise to results at once not contemplated and deleterious. These may be either generalized or local in their nature.

The systemic effects manifest themselves as the result of smaller quantities taken, in nausea, and an inclination to vomit, while larger quantities give rise to headache, a sensation of dizziness, and vomiting or diarrhœa with abdominal pains.

The local symptoms consist of an inflammatory irritation of the sound skin, an irritation which is intensified when the skin is altered by disease, and which is perhaps due to the carbolic acid or creasote, or perhaps to the empyreumatic

ingredients which are contained in the tar. As a result of this local irritation there occurs, according to Hebra* an acne of a hard, red, bullet-like nature, which may last as long as the influence of the tar continues. After the acne has once developed it yields very slowly, requiring an average of from two to four weeks for its involution, when, however, it disappears without any remnant of scars or pigmented spots. Hebra's modification of Wilkinson's tar and sulphur ointment (sulph. præcip., picis liquidæ, aa 180 parts; cretæ albæ, 120 parts; saponis domest., adipis, aa 500 parts), for scabies is liable to excite eczema, either by being spread over the sound skin, or by reason of the hypersensitiveness of some persons to ointments.

Urine voided after inunction with tar often shows changes which are probably due to the carbolic acid contained in the tar, which is thus shown to have been taken up into the circulation. Petters† has found the urine in such cases to be of a deep blackish-brown, and emitting the peculiar odor of tar. On distilling the urine with sulphuric acid, he obtained, in the distillate, besides carbolic acid, certain heavy, dark-brown oily drops resembling those of creasote. As bearing on this fact it should be mentioned that after the taking of carbolic acid, the dark urine which is occasionally voided contains hydrochinon, which is a product of the oxidation of carbolic acid.

As a point of diagnostic value may be mentioned the observation of Jacubasch, that after inunction with a tar ointment (tar 1 part, vaseline, 10 parts) in eczema, albumen was distinctly present in the urine, which disappeared with the suspension of the remedy, again to appear with its renewal.

OLEUM JUNIPERI EMPYREUMATICUM—OIL OF CADE.

The oil of cade, the product of the dry distillation of the juniperus oxycedrus, not infrequently, by its external application, excites an inflammatory action. Kleinhaus‡ who applied the undiluted oil, after the usual method, directly to

*Hebra, Lehrbuch der Hautkrankheiten, I., p. 594.
†Petters, Prager Vierteljahrschr., 1855, Jahrg. XII., Bd. 3.
‡Kleinhaus, Allgem. Medic. Centralzeit., 1863, No. 24, p. 185.

acute or chronic eczematous or impetiginous surfaces, observed that when the skin was even only partially inflamed, a pretty well defined swelling and redness with severe pain was developed as an effect of the oil, and that the hair follicles shortly afterwards appeared on the skin as nodules of the size of hempseed, an affection which is perfectly identical with tar acne.

Bazin observed in patients who had employed the inunction of oil of cade in psoriasis, an eruption of isolated or grouped papules, which were tolerably large, slightly confluent and hard, with an areola, particularly on such parts of the body as are well covered with hair. They were located on the skin with broad nodular bases, and terminated in a point and sometimes in a vesicle. At the point there was always found a black spot, which was due to the presence of a hair. These papules hardly ever went on to suppuration, and even when scratched pus formed only at the points. The seat of the affection is in the hair follicles. Bazin gave to it the name Cade-sycosis (*sycosis cadique*).

In many cases, according to Kleinhaus, the swelling and inflammation spread from the point of original application over a considerable area, when they may give the appearance of an erysipelatous dermatitis ; the lymphatic vessels and glands may even become involved in the inflammatory process.

Water dressings and soothing ointments are sufficient, in connection with the suspension of the application, to allay the slighter forms of this irritation first noted.

For the relief of the pain in the variety characterized by widespread dermatitis, warm baths are recommended, the patient remaining in them for from half an hour to an hour at a time ; opiates may also be given internally, in small doses. Kirchheim* has reported an observation which shows how, in consequence of extensive painting with tar, severe symptoms may be developed in many individuals. A soldier who suffered from eczema squamosum, was painted with tar on the extensor side of all extremities, once a day for three days. On the fourth day there ensued vomiting, headache, want of appetite and pain in passing urine. Then followed

*Kirchheim, Berlin Klinische Wochenschr., 1872, No. 19, p. 224.

watery exudations from the skin, presence of albumen in the urine, pains in the renal region, and, finally, anasarca and œdema of the lungs. The latter was cured. The other symptoms, which proved to be those of morbus Brightii, complicated with gastric catarrh, still continued for a relatively long period, and the œdema and the albuminaria disappeared only slowly.

An untoward effect of oil of cade, of rather secondary importance, is the brown coloring of the skin which it is difficult to get rid of. To obviate this the oil may be given in form of soap. For this purpose the following may be prescribed : Butyr. cacao. 12.0, Ol. cadini 9.0, Ol. lini, Lig. ammon. caustici. ää 4.0. Of this 4 to 10 grm., according to the size of the affected part, may be rubbed in. This soap may be easily washed off with water.

ACIDA.

The dilute, inorganic acids, as sulphuric, hydrochloric, phosphoric, nitric, and the fruit acids—citric, tartaric, etc.—cause by their long continued employment, disturbances of digestion. The appetite fails, the tongue becomes coated, the teeth ache, gastric oppression and eructations supervene, and occasionally there is salivation and diarrhœa.

Attending the prolonged use of dilute nitric acid there frequently occur, according to Mitscherlich*, erosions of the gums and tongue, the gums bleeding very readily, and the teeth becoming loose—symptoms which must be regarded as due to the local action of the acid.

ACIDUM CARBOLICUM.

The fact that in some persons the exhibition of carbolic acid even in medicinal doses is capable of causing general nervous disturbances, has been familiar since the drug was first employed. Déclat† observed as a result of its use, a slight headache which lasted for from 5 to 15 minutes, spreading over the entire head and returning with each repetition of the drug, being most intense in the frontal region in some persons, and in others being more severe in the occipital. Neumann noticed heaviness and fullness (eingenom-

*Mitscherlich, Lehrb. d Arzneimittellehre, Bd. III, p. 81.
†Déclat, Traité de l'Acide phénique, Paris, 1854.

mensein) of the head, weakness of the legs, dizziness, the appearance of rings before the eyes, a sensation as of crawling insects and profuse sweating, to follow the administration of the acid in the pill form.

It is only in later years that the profession have become aware of the fact that under certain circumstances exceedingly deleterious and even fatal consequences may follow the application of carbolic acid to wounds. Observers are almost unanimously of the opinion that idiosyncrasy on the part of the patient enters as a factor in such cases. The nature and extent of this idiosyncrasy are unknown but that it is the chief if not the sole influence in the causation of these untoward effects, there is no doubt.

Busch,* therefore, classes carbolic acid with those drugs which, while they are valuable in medicinal doses, are poisonous to certain persons, the reason for whose sensitiveness is not yet known, when taken in quantities which innumerable other persons may take without injury.

The absorption of carbolic acid may take place under any method of its administration. After the application of the acid either by frictions to the sound skin or by keeping it in contact with the surface of a wound or mucous membranes, it may be detected in the tissues, in the blood and in the secretions and excretions. Through either of these modes of application the condition to which the name of "carbolism" has been given may be induced, and by which is understood the abnormal action of carbolic acid induced by one or more doses of the drug.

Formerly the passage of brown or greenish brown urine, or of urine which, though light when voided, became of a blackish brown or deep black color when exposed to the air, was regarded as the most reliable criterion of carbolism. Bill held that the carbolic acid in the animal body is transformed into chinone and that this imparts to the urine the black color. More recently, however, the cause of the discoloration has been explained by Baumann and Preusse.† They showed by analysis of such carbolized urine that it contained hydrochinon, in the form of hydrochinon sulphuric acid,

*Busch, Berlin. Klin. Wochenschrift, 1880, p. 304.

†Baumann und Preusse, Archiv. f. Anatomie, u. Physiologie, 1879, p. 245.

in addition to this coloring matter. According to this view, a not inappreciable amount of the carbolic acid introduced into the body is converted, by oxidation, into hydrochinon. A portion of this is by further oxidation changed in the system into indefinite coloring matter which is excreted by the urine to which it imparts its color, but the major portion appears in the urine as hydrochinon sulphuric acid. The dark discoloration which in many samples of urine occurs only on standing, is caused by the splitting up of the eliminated hydroch. and the freeing in this manner of the hydrochinon, which, under the influence of the atmosphere, is oxidized into colored compounds. It follows from this that the greater the alkalinity of the urine the more rapidly does the change take place.

It has been established through accurate observations that this carbolized urine is not always pathognomonic of deleterious untoward action of the drug; it is more frequently the case that a number of but slightly characteristic but dangerous symptoms combine to constitute carbolism and to determine a fatal result. Kuster,* who demonstrated the poisonous properties of carbolic acid, particularly in antiseptic treatment of wounds, indicated as the reason why so few fatal results of the use of the drug are reported the fact that the uncertainty of the symptomatology has permitted the accidents to be classed as shock, collapse, etc. He observed a fatal termination in four or five of such cases. He mentions general debility and existing disease as predisposing to the occurrence of deleterious action of carbolic acid. Von Langenbeck† noticed a severe case of carbolic acid intoxication in a boy, abscesses in whom had been treated with a carbolic paste; in two other cases death followed the employment of the "dry carbolated dressing" of slight operations. Rose‡ also reported a case in which the application of carbolized cotton, which was moist and smelt very strongly of carbolic acid, was followed by gangrene of a finger, a wound in which had previously been healing kindly.

A case accurately observed by Busch (l. c.) may be mentioned here as characteristic of the symptomatology of carbolism: A boy suffering from an abscess under the trochanter was operated on for

*Küster, Berl. Klin. Wochenschr. 1878, No. 48.

†Langenbeck, eod. loco. 1878, No. 48.

‡Rose, Verhandlungen d. Gesellschaft d. Aerzte in Zurich, 19 Dec., 1874.

its relief. During the few minutes consumed by the operation he was kept under a two-per-cent. carbolic spray, and the wound was afterwards dressed with carbolic gauze. During the day following the operation he was seized with vomiting, which was attributed to the chloroform which had been employed. On the following morning the bandages were removed under the carbolic spray; during the day there was nausea, and in the evening there were symptoms of collapse and carbolic acid was detected in the urine. The pulse became small and frequent and the temperature sank to 35.5°C. The frequent vomiting made it impossible to administer remedies by the stomach, and in spite of the hypodermic and external application of analeptics, the boy died fifty hours after the operation.

Lücke* noticed nephritis as one of the local effects of carbolic acid; it disappeared, however, with the suspension of the drug. E. Wagner† investigated more accurately the changes in the kidneys. He applied carbolic acid to a case of gangrene of the leg and on the following day detected the drug in the urine. This latter contained numerous casts of medium width, and chiefly hyaline, interspersed with a few fatty and red blood corpuscles, or renal epithelia. A post mortem microscopical examination of the kidneys showed the uriniferous tubules to be dilated, their epithelia large, projecting far into their cavities and fatty, while the cavities contained numerous lumps of protoplasm and jagged glistening bodies.

In our opinion the influence of the spray has not been sufficiently regarded in the discussion of the question of the absorption of carbolic acid in the antiseptic treatment of wounds by means of carbolic acid. Olshausen‡ maintains that absorption is more apt to occur by the skin during the first carbolic acid dressing, and Langenbuch‖ holds that the liability to absorption through this channel, as compared with that which takes place from wounds, is underestimated, and believes that less is absorbed through the cleansing of wounded surfaces than is taken up by the normal skin. As facilitating absorption he mentions the soaping and shaving and scraping

*Lücke, Berl. Klin. Wochenschr., 1878, p. 248.
†Wagner, Deutches Archiv. f. Klin. Medicin, 1880, p. 509.
‡Olshausen, Berl. Klin. Wochenschr., 1878, p. 248.
‖Langenbuch, eod. loc., 1878, p. 414.

of the skin, through which the sweat glands are laid open, as well as the positive bathing of the skin with the carbolic spray.

The latter operates also in still another manner. It has been demonstrated by Röhrig* that finely pulverized watery solutions of substances are absorbed by the skin, which does not happen when the solution is simply laid upon it. The experiments bearing on this matter, performed under every conceivable precaution showed that when watery solutions of, for instance, the iodide and the ferrocyanide of potassium were applied to the skin in the form of spray, these substances made their appearance in the urine. It was also found possible to stupefy and to partially paralyze animals by solutions of morphia and woorara applied in the same manner, thus showing that substances may be introduced into the system, through the skin, more readily and in larger quantities when applied by means of an atomizer than when simply laid in contact with it. The opinion that a very large percentage of the carbolic acid in the carbolic spray is taken up by the skin, and particularly through the sweat glands, is thus fully justified. It also clearly follows that children, in whom the powers of resistance are naturally weak, are, under these circumstances, much more liable to carbolic poisoning than adults; the surface of the wound acted on by the spray bearing also in their case a much larger proportion to the surface of the body, a proportionately larger quantity of the carbolic acid is, *cetæris paribus*, taken into the system. The deleterious predisposing influence of soaping, brushing and shaving—manipulations also condemned by Lister—to untoward effects must, however, not be underestimated.

It clearly follows from what has been said that the introduction of carbolic acid into cavities lined with mucous membrane may be followed by carbolic poisoning. The administration of enemata containing carbolic acid, and the irrigation of the uterus and the vagina with the drug, are to be particularly considered in this connection. Thus Prætorius† observed buzzing, in the ears, dizziness, weakness, and attacks of fainting in a woman in whom the rectum was washed out with a dilute solution of carbolic acid, these symptoms supervening after a third of the following solution had been

*Röhrig, Physiologie der Haut, 1878, p. 116.

†Prætorius, Berl. Klin. Wochenschr, 1879. p. 214.

given : ¼ litre (℥ viij) of a one per cent solution in ⅓ litre (℥ x) of warm water. Kottmeyer* reports symptoms quite similar after the employment of an enema of a half per cent solution of carbolic acid in a lad suffering from oxyurides.

Olshausen (l. c.) noticed symptoms of profound intoxication after irrigation of the uterus, and Löhlein† observed, after two days, symptoms of poisoning in puerperal women, in whom vaginal and uterine injections were employed. Finally, Edwards‡ saw hiccup, nausea, chills, and anasarca, with diminution or suppression of urine, delirium and death, following the introduction of cotton tampons saturated with carbolic acid into the vagina. He attributes these symptoms to an acute nephritis and consequent uræmia, caused by carbolic acid.

The treatment of carbolism is to be varied with the manner of the introduction of the acid into the system. A directly antidotal procedure is usually without effect. Husemann and Ummethum recommend saccharated lime (Calcaria saccharata) as an antidote, the lime uniting with the acid to form an insoluble and comparatively innocuous compound. The sulphate of sodium, also, it is claimed, is antidotal through its union with the carbolic acid to form a non-poisonous phenol sulphate.

Should the drug have been introduced in an enema and only a short time have elapsed between such introduction and the employment of means of relief, irrigation of the bowel is to be commended as the first procedure. In the case of carbolism, as it is commonly observed, and due to absorption of the acid through the skin and the surface of wounds prompt symptomatic treatment of the general symptoms is indicated. The internal or hypodermic exhibition of excitants, energetic irritation of the skin by sinapisms and friction, and the fardaic current will be found valuable aids to this end. To combat the vomiting, small pieces of ice and vegetable astringents should be given.

THYMOL.

Thymol, contrary to carbolic acid, combines with its exceedingly antiseptic and antifermentative properties, which were first

*Kottmeyer, eod. loc. 1879, p. 501.
†Löhlein, eod. loc. 1878. p. 25.
‡Edwards, Virchow, Hirsch's Jahresber, 1869, I., p, 349.

demonstrated by the experiments of L. Lewin,* and which are by no means sufficiently appreciated, perfect safety in its internal and external use. Although it is used extensively for dressing of wounds, syringing of serous cavities and abscesses, etc., *no injurious effect upon the functions of the body has ever been observed.*

After the internal administration of a solution of 1 gramme (gr. xv) of thymol to 1,000 gramme (1 quart) of water, a burning sensation in the mouth and gastric region is observed as an untoward effect. Should the drug, however, be taken in substance or pills in large doses of 1 to 1.5 grammes (gr. xv to gr xxiij) within 24 hours, the burning in the epigastric region increases; the latter itself becomes tender on pressure and finally the burning sensation developes into pain, which may last several days after the drug has been discontinued. According to Bälz†, perspiration is sometimes observed and occasionally a transient buzzing of the ears and partial deafness. After doses of 2 to 3 grammes (gr. xxx to gr. xlv.) which produce a decrease of temperature of 2° C. (3-6 F.) Bälz observed, in rare cases, dizziness and delirium.

*L. Lewin Das Thymol ein Antisepticum und Antifermentativum, Virchow's Archiv. Bd. 65.

†Bälz Archiv der Heilkunde, 1877, p. 344.

ALTERATIVES.

HYDRARGYRUM.

Among the drugs which, through their extensive therapeutic application, are frequently productive of symptoms annoying to the physician, and still more so to the patient, mercury occupies a leading position. The affections which follow its internal and external administration are varied in their character. They comprise structural lesions of the skin and mucous membranes, as well as purely functional disturbances of various organs not traceable to any appreciable organic change, *e. g.*, of the salivary glands and parts controlled by the peripheral and central nervous systems. This condition has been enominated "hydrargyrosis' or mercurialism.

To obviate the numerous external inconveniences as well as the directly deleterious untoward effects, so frequently traceable to the traditional modes of the application of mercury, several new methods have of late years, and especially in the treatment of syphilis, been devised for the administration of mercury. The inunction of mercurial ointment, which was formerly applied in alarming doses—even to 500 grammes (℥ xvj) daily—is still productive of the greatest number of undesirable untoward effects, perhaps because of the fact that the quantities of mercury taken into the system through this means, are too small to destroy the syphilitic virus in a short time, or because the quantities absorbed through its long continued use, are, though small, sufficiently large to cause injurious effects in persons predisposed to the action of the drug.

The prolonged use of calomel is also, as has been demonstrated by Radziejewski,* sometimes accompanied by undesirable results, through its retention in the cæcum, where, by prolonged contact with the chlorides of sodium and ammonium, it is changed into corrosive sublimate and thus causes erosion and ulceration.

For this reason the plan of treating syphilis by hypodermic

*Radziejewski, Archiv. für Anatomie und Physiologie, 1870, p. 22.

injections of the bichloride of mercury, as introduced by G. Lewin,* and in which almost all the mercury is taken into the circulation, may be regarded as a veritable advance, though even in this manner of applying it untoward effects are occasionally noted. More recently two other combinations of mercury have been recommended by Bamberger† with a view to obviating the local irritation which so frequently follows the hypodermic employment of the corrosive sublimate. One of these is a solution of the albuminate of mercury, prepared by combining 100 ccm. (℥ iij) of a filtered solution of albumen (1 volume white of egg to 3 or 4 of water) 60 ccm. (℥ ij) each of a five per cent. solution of corrosive sublimate and a twenty per cent. solution of common salt, and 80 ccm. (℥ ijss) of distilled water. One ccm. of this solution, which becomes clear on standing two days, and filtering, contains 0.01 (gr. 1/6) of bichloride of mercury in combination with albumen. This solution causes no local irritation.

This author recommends even more highly a solution of peptonized mercury, prepared in the following manner: One gramme (15 gr.) of soluble, commercial peptone is dissolved in 50 grammes (℥ iss) of water and the solution filtered. To the filtrate add 20 ccm. (℥ v) of a 5 per cent. solution of corrosive sublimate, and to dissolve the resulting precipitate 15 to 16 ccm. (℥ ss) of a 20 per cent. solution of common salt. Sufficient water is added to the resulting solution to make 100 ccm. (℥ iij), which after standing for several days is filtered. Each ccm. of the solution contains 0.01 gramme (gr. 1/6) of mercury in the form of the peptone combination. The elimination of the mercury by the kidneys is said to be very prompt when this fluid is given hypodermically. The chief value is, however, ascribable to the method, the cure being more promptly effected through it and the system is thus kept under the influence of mercury for but a limited time.

We shall open our consideration of the untoward effects of mercury with a description of the

Changes in the Skin.—The affections which manifest themselves in the skin after the exhibition of mercury, in many persons, are erythema and eczema (eczema mercuriale). The latter was first noticed

*G. Lewin, Die Behandlung der Syphilis mit subcutaner Sublimatinjection, Berlin, 1869.
†Bamberger, Wiener medic. Wochenschrift, 1876, No. 11 u. No. 4, p. 1074.

by Benjamin Bell* and Pearson, while Alley† was the first to accurately describe these affections, and to apply to them the name hydrargyria. Hebra,‡ and Kussmaul‖ also, failed to recognize in it any characteristic peculiarity of either course or symptoms, and regarded it as identical with ordinary eczema, while Bouchardat regards it as a disease *sui generis*

According to older authors mercurial eczema, which ordinarily occurs after the external application of mercury, may also follow its internal exhibition. Thus Alley (l. c.) noticed it in an adult as a result of 0.12 gramme (gr. ij) of calomel, and in a girl as a result of 0.18 gramme (gr. iij) of the drug. Ascherson observed it in a young man after the injection of 0.24 gramme (gr. jv). More recently Fournier reported an exanthematous eruption, and Engelmann§ described a case in which after the injection of 0.45 gramme (gr. viij) of calomels, in doses of 0.15 gramme (gr. ijss), and two hours after the last dose, an erythema on the head, with symptoms of fever, swelling of the face, etc., began to develop. The eruption spread, in the course of a single night, over the whole body and was attended by a sensation of intense burning, itching and great debility. After four days it subsided and the skin of the face and breast peeled off in large flakes, as in scarlatina. The appetite and strength were restored very slowly. This same person declared that he had frequently before had the same symptoms after the internal administration of mercury.

Hebra, on the other hand, declares against the possibility of such a development of the exanthema, regardless of the preparation of mercury which may have been employed. It is, at most, very seldom met with and appears only in virtue of individual predisposition.

This eruption, however, not infrequently appears after the shorter or longer external exhibition of mercury, and especially after the inunction of blue ointment. In some it appears as a consequence of minute doses of the drug, while in others it does not occur after

*B. Bell, Treatise on Gonorrhœa virulenta and Lues venerea, II., p. 228.

†Alley, Observations on the Hydrargyria or that vesicular Disease arising from the exhibition of Mercury. Dublin, 1804.

‡Hebra, Hautkrankheiten I., p. 452.

‖Kussmaul, Untersuchungen über den constitutionellen Mercurialismus, Wurzburg, 1861.

§Engelmann, Berlin. Klin. Wochenschr, 1870, p. 647.

even large doses and their long continued employment. Alley found it to occur with twice the frequency in men as in women, which fact he accounts for by the additional fact that men find the necessity of employing of blue ointment much more frequent than obtains in the case of women.

Hebra defines eczema mercuriale as a disease of the skin characterized by a multitude of red tubercles, vesicles, or small pustules which are very thickly disposed. Alley distinguishes three forms of eczema which he classifies, according to the severity of the attack and the mode of their development, as follows: 1, Hydrargyria mitis; 2, Hydrargyria febrilis; and 3, Hydrargyria maligna. Such a differentiation is, however, very arbitrary, inasmuch as the three forms are identical in all essential particulars.

The exanthem sometimes occurs after but one, though more frequently after several applications of the blue ointment, and is attended by intense itching and burning, its seat being most frequently in the inner surface of the thighs, on the scrotum or vulva, and thighs, being seldom found on the upper extremities, back or face. In many persons the eruption is attended from its beginning to its disappearance with fever, headache, sleeplessness and gastric disturbances. The parts of the skin affected are covered with dark red spots of different sizes, and disappearing readily on pressure, which soon become confluent over a large surface, on which appear numerous vesicles of the size of a pin head, seldom larger, containing a fluid which is at first clear but later becomes opaque; these vesicles may either burst or dry up. Usually, after four or five days, the eruption, which sometimes resembles that of measles and again that of scarlatina, grows pale and the epidermis peels off either in branny scales or in larger flakes. Recovery is usually complete after from eight to fourteen days.

In some cases the patient suffers more severely, the whole body or large areas of it being affected with the eruption. In these cases, too, the fever runs high, and there is angina of the fauces; the numerous pustules either bursting spontaneously or having been scratched open, emit their irritating and ill-smelling contents which further aggravate the trouble, causing painful excoriation and swelling of the denuded skin and the formation of crusts. In such aggravated cases of eczema there is a repeated desquamation of the epidermis, and also, though rarely, a falling of the hair. The latter

fact is especially noteworthy, inasmuch as it is the only symptom referable to the skin, which is observable in animals which have been subjected to the long continued action of mercury.

In addition to these affections of the skin, mercury is also said, in very many cases, to cause by its external application gangrenous ulcers, and even to give rise to gangrene. We must, however, concur with Gwalter* that such an effect of mercury has not been satisfactorily proven.

Regarding the manner of the development of the mercurial exanthem, as a result of the inunction with blue ointment, nothing is definitely known. There are two possible methods of its occurrence, both being dependent on our conception of the manner in which absorption takes place. According to one theory the mercury applied by inunction is vaporized by the heat of the body, in which form it finds its way into the lungs and thence into the various parts of the body. Assuming this to be true, the affections of the skin which have been described can only occur secondarily, the drug being first taken into the circulation and there transformed into the bichloride or oxide of mercury. Should we, however, commit ourselves to the theory that the rubbing of mercury with fat converts it into an oleate, and that it is absorbed as such by the skin, we must believe that the eruption is due to the direct irritation of the drug. This irritation unduly prolonged may lead to a hyperæmia of the capillaries of the skin, with swelling of the epidermis and sebaceous glands, and give rise, as a result, to exudation, tubercles and vesicles. The latter is probably the usual, if not the only manner in which the skin disease is developed. This is the more acceptable view, since the oleic acid combinations with mercury, as, for instance, the corrosive sublimate, may produce their corrosive effects in this manner. On the other hand the rapid introduction of the preparations of mercury, even of the corro ve sublimate, into the circulation, as by hypodermic injection, does not give rise to either erythema or eczema. It appears from this that for the occurrence of the latter symptoms it is necessary that a soluble salt of mercury should act on the different layers of the skin, as is the case under frequent applications of blue ointment, which contains combinations of mercury with a fatty acid. This theory does

*Gwalter, Ein Fall von Quecksilber vergiftung. Inaug-Dissertation Zürich, 1877.

not, however, exclude the possibility of the occurrence of changes in the skin through the internal exhibition of mercury, as seems likely in view of later observations.

As an argument against the view of the specificity of the affections of the skin following the application, advanced by the anti-mercurialists, so-called, it is sufficient, without entering into subtle deductions, to direct attention to the numerous cutaneous eruptions referred to in this work, produced by substances of the most heterogeneous nature. These reveal a most complete analogy among themselves, and the only specificity which they have in common is a direct or reflex action on the skin.

The treatment of mercurial eczema consists in the immediate suspension of the drug, and the local application of emollients, as oil, ointments, or vaseline.

The second untoward effect of the employment of mercury, which calls for notice is the salivation or stomatitis which occurs in from 30 to 40 per cent. of all cases. In most cases in from 24 to 48 hours, and in rare cases in two or three hours, after the internal exhibition or external application of mercurial preparations in medicinal quantities salivation sets in, either alone or accompanied by redness, swelling, loosening and tenderness of the gums. Salivation may also precede the latter symptoms and may be so excessive as to amount to as much as five kilos (five quarts) during twenty-four hours, and continuing during the night, may deprive the patient of his sleep. It lasts generally from three to ten days, but may continue longer, and is attended by an offensive odor from the mouth and a subjective metallic taste. There is nothing characteristic in the saliva itself. Its specific gravity may rise to 1059 at the onset of the salivation, but falls later on. After a certain time it develops an offensive odor, is strongly alkaline in its reaction and acts as an irritant on the part over which it flows. The gums, the mucous lining of the cheeks and palate, the tongue, the soft palate and the tonsils undergo changes in degrees varying with the individuality of the patient, the duration of the exhibition of the mercury and the quantity administered. The changes may embrace all the stages from a simple hyperæmia to ulceration and necrosis of the tissue.

In the milder degrees of mercurial stomatitis the margins of the gums, which bleed very readily, are covered with a yellowish, slimy substance which emits a foul odor. The teeth may become

loose and the ulcers, which in the more aggravated forms manifest a disposition to spread both in depth and breadth, have generally even, dentated margins, and are covered at the bottom with a thin yellowish secretion. Not infrequently a swelling of the lymphatic glands of the neck is also observed.

The subjective general disturbances are very serious, even in the milder attacks of mercurial salivation. Sleep is prevented by the constant necessity of either expectorating the saliva or swallowing it. In addition to this there is the pain caused by the contact of the food with the inflamed or ulcerated parts. The swelling of the tongue, which is not an infrequent occurrence, interferes with articulation, all of which taken in connection with the febrile condition frequently present, the anorexia, headache and bodily weakness make the condition of the patient a very tormenting one. After this condition has existed for several days, the drug having been suspended in the meantime, the salivation begins to diminish in quantity and the morbid changes which have been caused in the mucous lining of the mouth begin to improve, and existing ulcers begin to heal, leaving, when the process is complete, radiate cicatrices. In cases in which the destruction of tissue has been excessive, several weeks and even months are required for complete restitution.

There are two circumstances which observation has shown to predispose to the occurrence of affections of the mouth, and particularly salivation, in mercurialization, viz.: 1, Uncleanliness of the mouth, and 2, a weak, anæmic constitution or serious antecedent disease.

The changes above indicated may also be excited by the hypodermic administration of mercury. This circumstance, taken in connection with the fact that mercury may be detected in the saliva, probably as an organic compound, proves that the drug is eliminated through the salivary glands, regardless of the manner of its administration. It is in this way that salivation and changes of the tissue in the cavity of the mouth are explained, since it must be conceded that the immense quantities of saliva which are secreted are due to either the direct irritating action of the mercury on the parotid and submaxillary glands, or to reflex nervous excitation of them, and furthermore that the saliva thus secreted, if it contain sufficient mercury, must, if its action on the tissue be sufficiently prolonged,

inflame or erode those parts of the buccal cavity which it bathes. It is to be observed that early infancy presents a certain immunity against the production of salivation in consequence of the administration of calomel. The reason for this immunity lies probably in the absence of chloride of sodium from the food (milk) which nurslings receive. A transformation of calomel into corrosive sublimate may thus either not take place at all or to a very slight degree. The susceptibility of this age, even to vapors of mercury, is exceedingly small. Grapin* reports that a woman, who, with her 14 months old child, was constantly exposed to mercury vapors, became sick with a severe stomatitis, whilst the child, though it was nursed by its mother, remained healthy. Oesterlen demonstrated by experiments, that young cats, which were treated with mercurial ointment, acquired neither salivation nor stomatitis.

The treatment of the mercurial affections of the mouth must, in the first place, be prophylactic. To this end it is necessary that patients should keep their teeth clean, and especially that they should remove from carious cavities the products of decomposition. Inasmuch as the poorly nourished have a special predisposition to these affections, care must be taken to secure proper nutrition. After the suspension of the mercury the exhibition of potassium chlorate, first recommended by Herpin, still occupies the first place among both prophylactic and curative measures. It affects most rapidly and most effectively the morbid processes in the mouth. It is given in a 2 to 3 per cent solution, employed as a mouth-wash and gargle, and also in quantities of from two to three grammes (gr. xxx to gr. xlv.), daily, internally. In cases of uncomplicated salivation an astringent wash (tannin, gr. xv to gr. xlv, in water ℥ jvss), is beneficial. Alum in solution (one to one and a-half per cent), may also be employed in addition to the potassium chlorate, as a mouth-wash. When inunction is being employed, Siegmund recommended the application of tar to the gums, both as a preventive and curative measure in stomatitis mercurialis. When the gums bleed easily they may with benefit be painted with tr. myrrhæ, with equal parts of tr. myrrhæ and tr. kino, or with tr. krameriæ. The latter substances may also be employed to cleanse foul ulcers of the mouth when it is preferable not to employ disinfectants, distinctively such as carbolic

*Grapin, Archives. génér., 1845, iv. p. 331.

acid in strength of 0.5—1.0 to 150 of water, or thymol 0.5 to 500 of water.

The untoward effects of mercury hitherto described are by far the most frequent of occurrence, and may succeed large and medium doses as well as small doses. Notwithstanding the fact that their duration is short they are classed with that collection of symptoms to which the term mercurialism has been attached. They merely indicate that mercury has been absorbed, that it is circulating in the system and that it is causing certain functional or anatomical changes on either its channel of entrance or exit. True constitutional hydrargyrosis or mercurialism, however, that is the condition of disturbed nutrition, sensation and even motion which seriously interferes with the economy of the system, and which most frequently follows the prolonged use of small doses, does not disappear so readily; it is due, probably, to elimination and deposit of the metal in the different organs. These symptoms obtain in their most characteristic form among workmen, who employ mercury regularly in their business, and are described in a classic manner by Kussmaul (l. c.) They occur less frequently as a result of the medicinal employment of the metal, and in the following consideration of the subject only such effects will be treated of as are indisputable, and no mention will be made of the exaggerated charges which have been urged by the opponents of the drug.

The disturbances of nutrition are always associated with changes in the general condition and are almost wholly provoked by direct effect of the mercury on the alimentary canal or its secretory glands, and not, as was formerly held, through some mysterious power it possesses of causing the organs to melt and the blood to decrease. There are several facts to prove that the stomach and intestines are affected.

G. Lewin (l. c.) observed symptoms of gastro-enteritis, pain and a burning sensation in the region of the stomach, especially on pressure, and diarrhœaic stools frequently tinged with blood as a result of the subcutaneous injection of mercury, and more particularly when the ordinary dose had been exceeded. Together with these symptoms the general condition of the patients was bad, they being pale, complaining of weakness, suffering from debility and having their sleep disturbed by frightful dreams. This effect on the intestinal

tract is explained in the belief that the metal is eliminated through this channel even after hypodermic exhibition of the drug.

Corroborative of the changes above indicated, as affecting the alimentary canal, might be adduced the experiments on animals as well as the post mortem appearances in man, revealing evidences of catarrh in its various stages, and even ulcerations, especially of the ileum and cæcum. The anorexia, emaciation, emesis, gastric and abdominal pains and decline of bodily health, frequently observed in those who have been subjected to a prolonged course of small doses of mercury, are explicable in the same manner. This explanation is especially satisfactory when it is remembered that the elimination of the metal, together with the tangible anatomical changes in the stomach and intestines above noted, causes an impairment of the activity of the digestive juices. In consequence of the gradual decrease or loss of appetite we find that such persons not only take a smaller quantity of food, but that that which they do take is assimilated much more slowly coincidently with the onset of a catarrhal condition of the intestines. Under certain conditions this assimilation is so slow that the nutritive processes are kept up at the expense of the body itself.

This conception of the matter is well sustained by the result of investigations of tissue metamorphosis by Von Boeck, in a syphilitic who had been treated by means of inunctions of mercurial ointment. He discovered no change in the decomposition of the albumen during the treatment. In this case, however, the operation of the mercury was continued only sixteen days—a period which is generally too short for the appearance of changes, of the nature of that described, in the digestive tract. It is necessary—and this is particularly to be borne in mind—for the occurrence of disturbances of nutrition, that there should either be a predisposition on the part of the patient or a prolonged action of mercury on the digestive tract.

As an accompaniment of disturbances of nutrition, and seldom appearing alone, there is a change in the urine which is an index to the condition of the kidneys. It not infrequently contains albumen although in but insignificant amount. Inasmuch as the kidneys, as has been demonstrated, are the channel through which a portion of the mercury is eliminated, the cause of the presence of the albumen is probably traceable to the irritation of the drug on the uriniferous tubules. The view that this albumen does not originate in structural

changes in the kidneys but is really the mercury which is thus eliminated in the form of an albuminate, is not supportable, the fact being that albumen is seldom found in the urine of persons under mercurial treatment, while the drug itself is constantly present. Albumen, however, appears when the drug is given in poisonous doses, and then also substantial changes in the urinary tract are demonstrable. Sugar has also, in addition to albumen, been found in the urine after the use of mercury. This was proven by the experiments of Saikowski* and Rosenbach† on animals. In this regard mercury bears a certain analogy to other poisonous substances as morphia, carbonic oxide, etc.

The therapy of the general disturbances of nutrition consists in the removal of the deleterious agent and in a suitable dietary. Besides this improvement in the hygienic condition of the patient, appropriate non-irritating food must be given, with a view to correcting the possible changes in the alimentary canal, and eliminating the drug as rapidly and completely as possible from the body. The latter may be effected by inducing active diuresis, by means of vapor and sulphur baths, but particularly, as recommended by Melsens,‡ by means of iodide of potassium, after the employment of which larger quantities of mercury are discharged through the kidneys than under ordinary circumstances.

The disturbances of nutrition and of the general condition described, as has been observed to be the case in chronic poisoning by other active metals, are frequently but the precursors of functional disturbances in the general nervous system. Occasionally some of the latter also appear during the course of the ordinary treatment by inunction.

The disturbances of sensation are evident not only in an alteration of certain physical attributes and affections, but also as demonstrable peripheric functional changes in the organs of special sense, as those of the sense of touch and pain, etc. The individuality of the person attacked plays an important part in this matter; in some persons we find nervous affections of a centric nature and of greater or lesser degrees of severity, while in others the disturbance manifests itself in the form of either peripheral anæsthesia or hyperæs-

* Saikowski, Virchow's Archiv. Bd. xxvii., p. 346.
† Rosenbach, Zeitschrift f. naturw. Medicin. 3. Reihe, xxxiii., p. 36.
‡ Melsens, Annal. de Physique et de chimie, III. S., T. 26.

thesia. The following central disturbances have been observed to follow the hypodermic injection of mercury: A condition of physical erethism, manifesting itself in a bad temper or increased irritability, or diffidence or bashfulness. These manifestations are associated with pallor of the countenance, asthmatic respiration, and even irregularity of the heart's action and great debility. These were first noted by Pearson after mercurial inunctions, and have been also noted by G. Lewin in individual cases. Bauer* and Kussmaul observed the most marked cases among the workmen engaged in the manufacture of mirrors. Kussmaul maintains that these symptoms are especially characteristic of the action of mercury. Their continuance may result in sleeplessness and other disturbances of the sensation due to increased excitability of the brain, especially of the cortical layer of the cerebrum, such as hallucinations and even delirium, which, however, are but temporary and cannot properly be classified as independent forms of disease.

There frequently appears pain in the joints, in the face and teeth, or, the converse of this, viz., paralysis of sensibility, may supervene, manifesting itself as veritable anæsthesia and analgesia.

In addition to these changes in the sphere of sensation there are other mercurial affections which manifest themselves as *disturbances of motion.* These are most frequently observed in the tremor mercurialis, which appears most frequently in the chronic form of mercurialism, but may come on paroxysmally. At first only the arms and hands are attacked, but in cases of the long continued action of the drug the lower extremities and the muscles of the trunk also suffer. An examination of the muscles thus affected with reference to their electric excitability shows them to be normal, though they may be reduced to a condition of great debility. In this regard as also in the absence of paralysis this mercurial affection of the muscles differs from that which occurs as a result of lead poisoning.

A sensation of dizziness which not unfrequently supervenes on the hypodermic and even epidermic administration of mercury would seem to imply a simultaneous disturbance of sensation and motion. In some of his patients to whom he had administered hypodermic injections of maximal quantities of mercury, G. Lewin observed marked debility and attacks of dizziness so severe as to necessitate

*Bauer, Ueber Mercurialismus Inaugural Dissertat. Erlangen, 1860.

the patients laying hold on something for support in order to prevent their falling. These vertiginous seizures with the symptoms of faintness, continued even after the patients were put to bed. The identity of these symptoms following the hypodermic injection of large doses of corrosive sublimate with the attacks of dizziness supervening on the long continued use of mercury, and which were formerly termed eclampsia mercurialis, is complete.

The symptoms, which are referable to the central nervous system are undoubtedly due to a direct influence of the mercury, which Kussmaul has denominated a brain poison, on the parts affected and in such a manner that the more transient symptoms manifest themselves in cases in which the drug is merely suspended in the circulation, while those of a chronic nature are due to a deposit of the mercury in the nerve centres and in the sensory and motor tracts. As supporting the latter statement we would refer to the observations of Pickel,* who, through dry distillation of the brain of a patient who had been subjected to prolonged mercurial treatment, was able to demonstrate the presence of the metal. Lauderer† made a similar demonstration in the case of a person who had been poisoned by mercury. There is, up to the present time, an absence of investigation with a view to determine the extent to which the metal thus effects a deposit in the spinal cord, and the peripheral distribution of the nerves. It must be conceded that the transient as well as the permanent changes induced by mercury are primarily due to changes of a chemical nature in the central and peripheral nervous tissue, although the changes may not be demonstrable under the microscope. Microscopical examination of these parts after the exhibition of mercury has, as yet, been productive of but insignificant results. Pleisch and Koch, respectively, found a darker color of the gray and white substance.

The prognosis of these affections, and particularly of tremor mercurialis, is dependent on the duration of their continuance. It may be favorable when this continuance has been of short duration, but it is doubtful, if not positively unfavorable, if the affection has continued for any considerable length of time.

The therapy must be conducted on the same general principles that obtain in the treatment of general disturbances of nutrition,

*Pickel, Buchner, Toxicologie, 1822, p. 433.

†Lauderer, Buchner's Repertor. III. Reihe, Bd. 25, p. 248.

and must be directed to the removal of the mercurial influence, and to the most complete elimination of the metal from the system. In addition to this cold frictions, douches and sea-baths, and in the condition of erethism, the use of nervines are indicated. The electric current might be tried in conditions of anæsthesia and analgesia.

ACIDUM ARSENIOSUM.

The similarity of the physiological action of the various compounds of arsenic extends to the untoward effects which attend the single or repeated exhibition of the drug. We shall, therefore, consider only the arsenious acid, which may be regarded as the typical preparation of arsenic.

Binz and Schulz* have recently shown that when arsenic acid is digested for several hours at a temperature of 38° C., with fresh fibrin, fresh brain substance, white of egg or pancreas, it appears in the dialysate as arsenious acid. They also demonstrated the presence of arsenious acid in the fluid contents of the intestines in animals after the exhibition of arsenic acid, and, *vice versa*, the presence of arsenic acid after arsenious acid had been introduced. According to these observers the processes of oxidation and reduction take place in the glands, in the protoplasm of the nerve centres and in all other cells in which the conditions for the development of such action obtain. Through this continual exchange of nascent oxygen in the molecules of living albumen the oxidation of the living cells is more active than obtains in the case of normal tissue change, and it is upon this local increased oxidation that all the phenomena of the effects of arsenic depend.

This explanation, also renders more comprehensible a portion of those phenomena which appear as a result of the internal or external exhibition of arsenic, and which lie beyond the domain of physiological action. It is especially applicable as an explanation of the influence which is exerted on the skin of both man and animals by the internal administration or external application of the drug. The ancient physicians were even familiar with this *modus operandi* of mercury. Thus Paulus Aegineta† writes: "Arsenici vis

*Binz and Schulz, Archiv für experimentelle Pathologie und Pharmakologie, Bd. XI., p. 200.
†Paulus Aegineta, Opera ed J. Guinterius, Lugduni, 1551, p. 479.

est caustica, utuntur eo in pilis abolendis, quod si diutius adhæserit etiam cutem ipsam attingit." The application of arsenic to the healthy skin, either in a watery solution, or as an ointment or paste, and maintained in contact for some time, gives rise to an inflammatory action, attended by a stinging or burning pain and a slight fever, and vesicles or pustules may develop on the reddened surface without the appearance of any symptoms of general absorption. Should the inflammation, however, become aggravated there may set in, according to Falck,* an erysipelatous swelling upon which may appear a discolored sanguinolent eruption which may mark the beginning of general poisoning, after the same manner, as will presently be described, that these also appear as a result of the internal exhibition of the drug. The same results follow the application of the drug to the surface of wounds. The hair generally falls out on affected parts. The exanthemata heal through the shedding of the epidermis of the inflamed surface, in the form of large flakes.

Changes of different kinds, but of an analogous nature, have been observed to follow the internal exhibition of arsenic in ordinary medicinal doses, and especially when given in the form of Fowler's solution. The variety which these changes may assume is manifest in the, it must be confessed, somewhat homœopathic description of Imbert-Gourbeyre:†

"Eruptions pétéchiales ou ecchymoses éruptions papuleuses ortiées, vésiculeuses, érysipélateuses, pustuleuses . . . . telles-sont les principales formes de l'arsenic, exanthématogène dans ses manifestations a la peau." According to this, individual authors vary in their descriptions of arsenical eruptions. Thus Macnal‡ reports an eruption resembling that of measles in a case to which he had for only three days given 0.18 gramme (gtt. iij) of Fowler's solution. Pareira observed, in a gouty patient for whom he had prescribed 0.01 gramme (gr. ⅙) of the arseniate of potash daily, on third day and after a restless night with headache and a sensation of increased warmth of skin, a very red eruption of the face, neck, the upper part of the trunk and flexor surfaces of the joints and likewise an œdematous condition of the eyelids. The eruption

*Falck, Die klinisch wichtigen Intoxicationen. Virchow's Pathologie und Therapie, Bd. I., p. 254.

† Imbert-Gourbeyre, Gazette, médic. de Paris. 1862, p. 227, und Etude sur quelques symptomes de l'arsenic. Paris, 1862.

‡ Macnal, Medical Times and Gazette, 1868.

disappeared between the second and fifth day, while desquamation in the form of flakes continued for nearly two months. The administration of arsenic after all these symptoms had disappeared aroused them again, when they were also accompanied by salivation. The eruption, according to Imbert-Gourbeyre, appears by preference on the neck, face and genitals, but likewise on the hands. The papules which constitute the eruption are of the size of a pin's head, at first distinct in groups but later becoming united and forming patches of the size of a lentil or larger. He also, like Pareira, describes the eruption as lasting from six to eight days, but observed only a branlike desquamation of the epidermis.

The minuteness of the dose which is sufficient to cause an eruption is exemplified in a case reported by Bazin,* in which erythematous pustules were developed after the exhibition during fifteen days of 0.05 gramme (gr. $\frac{5}{6}$) of arsenic.

A report by Wyss† of the case of a boy in whom he noted an area Celsi (porrigo decalvans) after the prolonged internal use of arsenic is of interest in this connection. He makes use of this observation to establish the view that this affection is due to a disturbance of nutrition in the hair follicles and not, as has recently been maintained, to the development of a fungus.

A contemplation of the effect of arsenic on the skin, as here detailed, must confirm one in the view that the changes which are induced by the internal and the external exhibition of arsenic are identical. In such case there must, therefore, after the internal administration of arsenic in many persons, be a permeation of the skin and also a partial elimination of it through this organ. This is in fact the case, as has been demonstrated by various authors.

Chatin‡ succeeded in demonstrating the presence of arsenic in the contents of a blister which was raised by cantharides on a person who had been poisoned by arsenic. Barella‖ established the fact of direct elimination of arsenic through the sweat glands, particularly when the skin acted vicariously for the kidneys, while Bergeron and Lemattre § showed that the arsenious acid combinations with the alkalies may be eliminated with the perspiration, but that

*Bazin, Leçons sur les affections cutanées artificielles. Paris, 1862, p. 196.
†Wyss, Archiv für Heilkunde, Bd. xi, 1870, p. 17.
‡Chatin, Journ. de Chimie Médicale, 1848, p. 328.
‖Barella, Journ. de Médicine de Bruxelles Juillet, 1863.
§Bergeron and Lemattre, Archive génér. de Medecine, 1804, vol. ii, p. 173.

the combination of this acid with iron is so split up in the system that the iron is given off in the urine, the arsenic appearing as an arsenite of potassium in the perspiration.

In the light of these facts we are constrained to regard the affections of the skin which we have considered, as due to the direct local effect of the arsenic, and that regardless of the manner of the exhibition of the drug, and we must, furthermore, with Binz and Schulz, seek their causation in an increased local combustion in the living cells.

Inasmuch as the arsenical eruption, as has been remarked, disappears spontaneously in several days, any medical means for its relief are scarcely called for. In cases in which the dermatitis has spread at all extensively or has assumed a malignant character, it will be found necessary, in addition to the administration of diuretics with a view to eliminating the drug through the kidneys, to resort to local antiphlogistic applications, and, in the event of the presence of the products of decomposition to apply antiseptics.

The internal employment of arsenic for a longer or shorter period is, conditioned on the individuality of the patient, more frequently followed by irritation of the mucous membrane of the mouth, throat and stomach, and consequent digestive disturbances, than by the symptoms detailed in the foregoing. The tongue under such circumstances is heavily coated, and there appears a disagreeable burning in the mouth, thirst, oppression in the region of the stomach, anorexia, belching and even vomiting. The mouth affection may assume the form of either angina or stomatitis. Very small doses of arsenic are also not infrequently productive of profuse salivation. Harles* was the first to note this fact, which he did in the following language: "Diutius continuato arsenici usu satis parco excitatur haud ita raro salivæ aliquanto largior secretio, sive ptyalismi levior species." More recently Imbert-Gourbeyre, Trousseau and Morganti† have, among others, reported similar effects.

This irritation of the mucous membrane of the mouth not infrequently extends to the respiratory passages, and we then have a dry cough, bronchitis and hoarseness.

*Harles, De usu arsenici, Norimbergæ, 1811, p. 301.
†Morganti, Gaz. Médic. de Paris, 1852.

Should the nasal mucous membrane be attacked we have a burning sensation in the nose, coryza, a dry catarrh, or in rare cases, as was first noted by Heim,* epistaxis. Should the mucous membrane of the nose, the tear ducts and the conjunctiva become involved through an extension of the catarrhal process (and this happens quite frequently) we have lachrymation, photophobia, amblyopia, swelling of the eyelids and the other, including the objective, symptoms of conjunctivitis. An icteric discoloration of the sclerotic—a quite common symptom in xanthopia from arsenical poisoning—is very seldom observed.

In some persons headache, buzzing in the ears and dizziness occur as evidences of nervous disturbance.

It remains to be mentioned in conclusion, that certain French authors, as Charcot† and Devergie‡ have advanced the statement that anaphrodisia not infrequently occurs as a result of the use of Fowler's solution. This suspension of sexual instinct disappears on the discontinuance of the drug.

The treatment of the symptoms detailed consists in a prompt suspension of the drug and the administration of demulcents to the mucous membranes affected. Inasmuch as all of the pathological processes disappear in a short time after the discontinuance of the drug, it is scarcely necessary to institute any antidotal treatment, such as the exhibition of hydrated magnesia or the hydrated sesquioxide of iron.

It is necessary, from a prophylactic point of view, that arsenic should not be given on an empty stomach, that the ordinary doses be not too rapidly increased, and, above all, that the use of drug should not be too long continued.

AURI CHLORIDUM. AURI ET SODII CHLORIDUM.

The chloride of gold, as also the officinal chloride of gold and sodium which was much employed and highly praised as a specific in syphilis‖, very frequently, according to the observations of Chrestien,§ and in doses of even 0.003–0.006 (gr. $\frac{1}{20}$ to gr. $\frac{1}{10}$), gives

*Heim, Vermischte Schriften, 1836, p. 302.
†Charcot, Bullet. de Thérapeut. lxvi., p. 529.
‡Devergie, Eod. loc. lxvii., p. 175.
‖Legrand, Bulletin de Thérapeutique, Décembre, 1846.
§Chrestien, De la méthode iatraleptique IIième édit. Paris, 1803.

rise to a feeling of heat and burning in the skin, gastric disturbances, colic and diarrhœa. The chloride of gold and sodium causes, even in doses which are below the standard maximum dose, according to Wibmer, headache, sleeplessness, dryness of the mouth, a feeling of oppression in the region of the stomach and diarrhœa. Others have noted in increased flow of urine, salivation and increased sexual power, as a result of the use of this drug.

The gastric disturbances referred to are explained in the gold salts and by the ready solubility of the double compounds of the chlorides of gold and sodium in the alkaline chlorides. They manifest the closest similarity to the disturbances observed as effects of other powerful metals, and are due to the irritation of the tissues, the mucous membranes of the primæ viæ more particularly, by the by the ingested drug.

PHOSPHORUS.

Even a single small dose (0.002 gramme [gr. $\frac{1}{30}$]) of phosphorus is capable of causing in some persons, who, for personal reasons, cannot tolerate the drug, nausea and vomiting, with a feeling of oppression or pain in the region of the stomach, diarrhœa attended with tenesmus, and in rare cases jaundice which may last, it is said, for weeks and even months. The variability in the operation of this drug is, perhaps, due in some cases also, to the manner of its exhibition, inasmuch as phosphorus taken in the form of pill or in oil remains longer in the stomach than when it is given in a menstruum, which facilitates its absorption, as chloroform, etc., and this long continuance of the absorptive process predisposes to the irritation of parts with which the drug lies in contact. Through an avoidance of this cause of irritation, by dissolving the drug in a solution of chloroform and administering it in capsules, Dujardin-Beaumetz* was enabled to employ it uninterruptedly for from eight to ten days, and in doses of from 0.003–0.004 gramme (gr. $\frac{1}{20}$–gr. $\frac{1}{15}$), before any symptoms of digestive disturbance developed, and such symptoms as then ensued disappeared with the temporary suspension of the drug or the diminution of its dose. Felix,† who treated methodically certain pulmonary affections,

*Dujardin-Beaumetz, Wiener Medicinische Wochenschrift, 1868, p. 767.

†Felix, De l'action physiologique et therapeutique du Phosphor pur. Bruxelles, 1881, p. 91.

as emphysema, tuberculosis, etc., with phosphorus, cautions against the employment of excessive doses. The commencing dose, according to him, should be 0.0005 grammes (gr. $\frac{1}{120}$) and gradually increased to 0.003 gramme (gr. $\frac{1}{20}$). He recommends the emulsion and the pill, made with a combination, in each dose, of 0.01—0.02 gramme (gr. $\frac{1}{6}$ to gr. $\frac{1}{3}$) of muriate of morphia, as the more eligible forms of administration. Should untoward effects occur in spite of these precautions, the milk of magnesia (carbonate of magnesia given in gum-water) should be given as an aperient. Small doses of bismuth subnit. with opium may be given for the gastric pains.

IODINIUM.

In consequence of the extraordinary curative powers of iodine and its compounds, and on account of its peculiarly wide range of therapeutic application, the attention of physicians was, even at an early day (1820), called to certain changes in the body which occasionally occur as a result of the exhibition of the drug. It was, it is true, a considerable time before these were recognized as the untoward effects of iodine, and the controversies as to the existence of such a thing as an "iodine disease," or "iodism," or whether the symptoms are traceable to other causes, fill many a page of the literature on pharmacology. Goitre, in particular, among other diseases, was formerly subjected to internal and external treatment with iodine, and consequently the abnormal effects of the drug were frequently observed in connection with this affection. As a result of this fact there was no lack of authors* who denied the occurrence of such effects of the drug when it was given for other affections, and also attributed the symptoms which occur during the iodine treatment of goitre, to "the absorption of the organic substances present in the goitre." But the occurrence of iodism was also combatted on more common sense grounds. Thus Hjaltelin† instanced the fact that the inhabitants of Iceland, particularly those living on the coast, employ as a principal article of diet the algæ, belonging to the class of laminaria, which are so rich in iodine as to cause them to constitute a source from which the drug is manufactured. Many

* Röser, Ueber die sogen. Jodkrankheit, richtiger Krankheit der vertriebenen Kröpfe Würtemb. Medic. Correspondenzbl. 1844, No. 31, und Arch. f. physiol. Heilkunde, Bd. VII. 1848, p. 74.

† Hjaltelin, Allgem. Medic. Centralzeitung, 1853, p. 745.

persons consume as a diet from 200 to 250 kilos (437 to 457 lbs.) of these dried plants annually. Since 50 kilos of these algæ yield at least 250 grammes (℥ viij) of iodine, these people consume an aggregate of from one to one-and-a-quarter kilo (2⅕ to 2½ lbs.) of iodine, equal to about 1½ kilo (3¼ lbs.) of iodide of potassium, annually. In spite of this large consumption of iodine, Hjaltelin was unable to discover any symptoms of iodism. But although the inference from these facts is clear, they should not be accepted as conclusive, for, not to mention the fact that the proportion of iodine contained in the algæ as here stated is five times greater than it really is, it must be remembered that, as in the case with other vegetables, only a small proportion of them is taken up by the fluids of the system, much the largest portion being discharged with the fæces as refuse. It will thus be seen that these coast dwellers appropriate only a very minute proportion of the iodine, which is very firmly incorporated in the plants. It would lead us too far to recount at this place, all the other objections which have been raised in this connection. It is now a well established fact that iodine and its salts, by its single or repeated internal or external administration, in doses of different size, are capable of causing changes in various organs, or in the general system, but only in those who are peculiarly susceptible to its influence.

The external application of only such preparations of iodine as contain the iodine in a free state, is productive of deleterious untoward symptoms. Preparations of this nature are such ointments of iodide of potassium as have turned yellow, Lugol's solution or the

Tincture of Iodine. The physiological local action of the tincture of iodine upon the healthy skin, the mucous membranes, and serous cavities is familiar. It is identical with that of iodine vapor. The sound skin is reddened by the irritation which it causes, and there is a feeling of heat which developes into a burning and pricking sensation; at first it becomes yellow but under repeated applications the color becomes of a dark brownish red, when it dries up and becomes wrinkled and eventually peels off in flakes. Associated with this normal effect there are, not infrequently, incidental symptoms either in the immediate seat of application or at some remote part, such symptoms taking the form of an exanthematous affection, resembling measles, or of a papular, pus-

tular or even vesicular nature which soon heals, with desquamation, on suspension of the drug. Thus A. Simon and Regnard* among others observed after the inunction of tinea capitis in children with a mixture of iodine and glycerine, the appearance of an extensive papular eruption on the face and other parts of the body. This observation is verified by Badin.† He could never cause albuminuria in adults by painting the skin with iodine, while its application to a normal surface no larger than can be covered by the hand, has excited this affection in children eight or nine years of age. He assigns the cause of this difference in effect to an increased facility of absorption in the skin of infants. This increase of absorptive power permits of the entrance of iodine as such into the circulation, while in adults, in whom it is absorbed more slowly, it enters the system in the form of the iodide of potassium or sodium. This explanation is, however, not satisfactory in view of the disturbances, which will be described below, which the iodide of potassium induces in the urinary organs. In addition to this an observation of Jacubasch‡ must be adduced as evidence against this limitation of the appearance of albuminuria. He noted the appearance of albumen in the urine, not only in children after painting them with iodine (for the relief of psoriasis, swelling of the glands, etc.), but also in a girl twenty-five years of age to whom an extensive application of the tincture of iodine had been made for the relief of an abdominal enlargement. The albuminuria appeared and disappeared in this case with the application and suspension of the drug. Zesas§ reports a still more remarkable case, which occurred in a patient forty-one years of age, and in which albumen was observed in the urine after four applications of iodine to an inflamed knee. This disappeared with a discontinuance of the iodine, but returned again after the drug had been reapplied for three days.

It is self-evident that the local effects of this drug on such portions of the skin as are deprived of their epidermis, and on the mucous membranes and the surface of wounds, must be more intense, as must also be the local changes and subjective symptoms

*Simon u. Regnard, Gaz. Médic. de Paris, 1874, p. 262.

†Badin, De l'albuminurie consécutive aux applications de teinture d'iode chez l'ent. fan Paris, 1876.

‡Jacubasch, Charité-Annalen Jabrg. vi, 1881.

§Zesas, Wien. Medicin. Wochenschr. No. 18, 1882.

thus induced. The pain which results from the irritation, which may even amount to cauterization, although very transitory in its nature, is nevertheless very severe. The iodine coagulates existing secretions of wounded surfaces and serous cavities, through direct combination with the albumen or albuminoid substances which they contain, and may thus excite active inflammation with consequent exudation or suppuration. In such event eruptions may also appear on remote parts of the body. This circumstance proves the fact that iodine may be absorbed from the place of its application, and after its absorption act on the skin.

But absorption after its external application manifests itself in another and still more unpleasant manner, viz., by the appearance of more remote effects on certain organs and their functions, as also through a series of general constitutional symptoms. These are, therefore, in a measure identical with the symptoms which frequently present after the internal exhibition of the compounds of iodine. Simon and Regnard (l. c.) saw coryza and epistaxis occur, in addition to the papular eruption already mentioned, as results of the inunction of iodine. They, moreover, also observed in fourteen cases four cases of albuminuria in connection with the presence of iodine in the urine. The albumen disappeared and reappeared with the suspension and renewal of the drug. Buckell* reports the case of a lady in whom a very light application of the tincture of iodine to a tumor occurring between the thoracic and cervical vertebræ, was followed by pain and a feeling of oppression in the epigastric region, with trembling, weakness, profuse perspiration, dribbling of urine and inability to maintain the erect posture. The administration of analeptics and the application of warmth to the epigastrium caused the symptoms to disappear after several days. Nélaton† injected two syringefuls of a dilute solution of iodide of potassium into a cold abscess, after having emptied it of its contents. In two hours there occurred disturbance of vision, vomiting, a thread-like pulse, swelling of the upper eyelids, pain in the larynx, and on the following day aphonia, a croupous cough and prostration. Under the application of ice, sinapisms to the extremities, vesicants to both sides of the neck, and laxative pills, these symp-

*Buckell, The Lancet, 1. Febr. 1843.
†Nélaton, L'abeille Médicale, 15 Novembre, 1853.

toms disappeared after three days. Fonssagrives* observed a similar case. In two hours after the injection of a small quantity of a solution of half the strength of the officinal tincture, into a tunica vaginalis traumatically inflamed—its fluid contents having been previously evacuated—he observed a swelling of the scrotum accompanied by considerable fever. Against the following day there had developed irritation of the bronchi, a nasal catarrh, reddening of the eyes, œdema of the epiglottis and salivation. The fever continued for five days. The more or less prolonged internal exhibition of iodine in medicinal doses gives rise to a greater variety of untoward effects than the more acute symptoms which result from the external application of the drug. Inasmuch as the iodide of potassium is much the more frequently employed when it is desired to secure the effects of iodine on the system, we shall consider it in lieu of all the other compounds of iodine.

POTASSII IODIDUM.

The first comprehensive treatise on the subject of "iodism" was prepared by Rilliet.† He differentiated three forms of the affection. The first, according to his opinion, occurs in all persons and at all ages after large doses, and is due to irritation of the gastro-intestinal tract by the iodine. The second is conditioned on a certain predisposition in individual organs, and manifests itself in the gradual appearance of slight nervous disturbances and anomalies of secretion of various mucous membranes and in affections of the skin. The third form is known as iodine cachexia or constitutional iodism. It embraces a series of general constitutional disturbances and disturbances of the nutritive functions, and appears as a result of the prolonged use of minimal doses of the drug. Practical observation has, however, shown that such a dogmatic division is not possible, inasmuch as sometimes one and sometimes another group of symptoms present, and small doses may arouse untoward action in one person which can be made to appear in others only as a result of large doses, and vice versa. It may be stated, therefore, that sometimes one organ and sometimes another is disturbed in its functions or

*Fonssagrives, L'Union Medicale, 1860, No. 71.
†Rilliet, Bullet. de l'Academie de Médec., 1860, p. 382.

suffers material changes through the action of iodine, and that the cause of these disturbances is unknown. We are not able, however, to deduce from this any rule, the conditions necessary to the development of these affections being unknown. We must, therefore, be content to consider the variable symptoms of the effects of iodine on separate organs in their details. Similar conditions supervene on the ingestion of the iodine combinations, notably the iodide of potassium, a fact which M. Rosenthal* demonstrated by means of experiments on himself, administering the drug by means of enema. Absorption takes place rapidly from the mucous lining of the intestines even when the drug is given in a diluted solution.

Following the ingestion of the iodide of potassium many persons, and particularly in the morning after waking, experience an astringent, metallic, bitter taste on the tongue. This may be made to promptly disappear, according to Laroche,† by rinsing the mouth with cold water to which a tablespoonful of spiritus cochleariæ has been added. In addition to this there is observed, in particularly sensitive persons, as an effect of small doses, scratching and burning and a sensation of dryness in the throat, and a sense of constriction of the pharynx. In rare cases an impairment of the ability to swallow has also been observed. The sensation of burning may extend from the throat along the sternum to the region of the stomach. Associated with this there is frequently increase in the secretion of saliva, in consequence of the peculiar property of the iodide of potassium to increase the secretion of nearly all the glands.

Although the functions of the stomach are not affected by one or more small or moderately large doses of the potassic iodide, the appetite being sometimes even stimulated thereby to a degree of intense hunger, nausea and vomiting are nevertheless occasionally excited in persons having a pronounced aversion to the drug, while in others, as observed by Ricord,‡ there is a pain referable to the fundus of the stomach, which is increased by pressure, but which has no influence on the digestion. Rabuteau ascribes this phenomenon to an adulteration of the potassic iodide (KI) with the potassic iodate (KIO_3). In this case, according to this author,

*Rosenthal, Sitzungsbericht der Wiener Akademie, Band XLVI, Abth. II.
†Laroche, Canstatt's Jahresbericht f. d. ges. Medicin, 1844, iv., p. 195.
‡Ricord, Bulletin Générale de Thérapeut., 1842, p. 161.

iodine is set free through the influence of the acids of the stomach, and thus attacks the mucous membranes. Though this hypothesis is not strictly tenable, these symptoms being also sometimes observed after the exhibition of pure iodide of potassium, it is nevertheless possible that in some persons the freed iodine conduces to the development of the symptoms as above. In view of this possibility, the iodide of potassium should be tested for the iodate, in the manner to be hereafter described, as soon as there exists any doubt as to the purity of the drug.

Disturbances of digestion supervene only after large and long continued doses of the iodide of potassium.

On the other hand, the irritative effects of the drug on the mucous membrane of the air passages develop so readily, that the majority of those who take it suffer from them to a greater or lesser degree. This irritation extends, in the first place, to the mucous membrane of the nose, but often simultaneously attacks the mucous lining of the larynx, bronchi and their divisions.

Since this effect on the nose was first observed, the name "iodine catarrh" has been attached to it. It manifests itself in inflammation, of varying degrees of intensity, of the mucous membrane of the nose, and may spread over the whole extension of this membrane, involving the posterior nares, frontal sinuses and antrums of Highmore. The mucous membrane of the nose becomes soft and spongy, and secretes quite freely, and the subjective symptoms, which often begin with a burning sensation in the nose, take the form in their further course, of a sensation of oppression, occlusion, sneezing, etc. Should the regio olfactoria be most decidedly affected, loss of the sense of smell may ensue. The affection disappears shortly after the suspension of the drug.

In the description of the acute pathological symptoms caused by the external application of iodine, the occurrence of œdema of the glottis has already been referred to. The tendency of the compounds of iodine to produce catarrhal effects on the mucous membranes, makes it probable that œdema of the glottis is traceable to an acute swelling of the mucous membrane of those parts, with consequent infiltration of the submucous connective tissue. The irritation of the mucous membranes of the lower air passages, supervening in many persons on small doses of the iodide of potassium, may also be adduced in support of this view. Thus Ricord (l. c.) often

observed a bronchitis, which was demonstrable on physical examination, accompanied by labored respiration, cough, with asthmatic breathing, pain in the chest, and quite free expectoration, which, however, never became purulent. Some authors* have, without sufficient warrant, classified these difficulties of breathing as "iodine asthma," after a manner analogous to the classification which was formerly made of the disturbances of respiration following the employment of lead, mercury, and other heavy metals. But even true œdema of the glottis may be caused by medicinal doses of iodide of potassium, as has been demonstrated by Petitjean,† although only in those who had been suffering from laryngeal affections previous to the treatment with iodide of potassium. In case of a person deceased in consequence of such œdema of the glottis, small ulcerations were found in the larynx, as well as œdema of the epiglottis. That existing lesions may become aggravated in this manner is shown by a case reported by Rodet,‡ in which a man, in whom tuberculosis was suspected, had more or less copious hæmorrhage after each dose of the iodide of potassium.

By the transmission of the catarrhal irritation to the vocal cords phonation may even be interfered with, in very rare cases, without the existence of deeper lesions.

Pathological changes of a nature analogous to those occurring in the mucous membranes, already referred to, may quite frequently appear in the eyes and their appendages, after the use of the potassic iodide. These seldom appear alone, occurring most frequently in an acute form in one or both eyes in connection with the iodine catarrh, or bronchial catarrh of similar origin, and manifest themselves also simultaneously, partially in catarrhal irritation of the connective tissue as well as of the lining of the lachrymal sac and duct. The vessels of the conjunctiva palpebrarum and conjunctiva scleræ are greatly injected, the mucous membrane is itself swollen and loosened, there is lachrymation but only occasionally photophobia. On the other hand chemosis and œdema of the eyelids now and then occur. The subjective symptoms vary with the degree of the affection. The patient usually complains of burning

*Santlus, Deutsche Klinik, 1856, p. 18.

†Petitjean, Accidents du côté de la peau et des mucueuses déterminés par l'administration de l'jodure de Pôtassium, Paris, 1879, p. 29.

‡Rodet, Gazette Médicale de Paris, 1847, p. 946.

and itching and of the sensation of a foreign substance in the eye. In some there is also a painful sensation of pressure in the supraorbital region at the foramen of exit of the supraorbital nerve.

These untoward effects of the potassic iodide may, according to the specific disposition of the individual, supervene after the exhibition of one or repeated doses. They most frequently appear after the repeated use of small doses, and disappear spontaneously in a few days after suspension of the drug, and without leaving any after-effects; their disappearance is facilitated by the application of compresses wet with slightly astringent lotions. Cases in which the symptoms, as above described, have come under observation after the use of only 0.5 gramme (gr. vijss) of the iodide of potassium have frequently been reported. Thus Mecklenburg,* among others, observed in the course of a few hours after the exhibition of 0.5 gramme of the drug, violent pain in the eyes, profuse lachrymation, a burning sensation in the nose and throat, and a swelling and livid discoloration of the upper eyelids and especially in the tarsal region. After the expiration of twenty-four hours these symptoms disappeared. The renewed administration of only 0.25 gramme (gr. jv) of the drug caused the same symptoms, with the exception of the swelling of the eyelids, to reappear within four hours.

Besides these more external symptoms there occurs, though very rarely, as a result of the use of the potassic iodide, a lessening of the power of accommodation, decrease in the acuteness of vision, and, in short, the symptoms of presbyopia. Corlieu† reports a case of this nature, in which, besides other abnormal effects of iodine, presbyopia with dilatation of the pupils and a suddenly occurring hypermetropia were observed. These symptoms disappeared in a few days after the discontinuance of the iodine. Dorval‡ observed diplopia and weakness of vision, and Brera, § dullness of vision and orbital pain. Which of these possible factors has been active in the causation of these functional disturbances, has not, as yet, been determined.

The symptoms of irritation of the skin mentioned above, and their effects on more remote parts of the body after the external use

*Mecklenburg, Berl Klin. Wochenschr., 1866, p. 262.
†Corlieu, Gazette des Hôpitaux, Juin, 1856.
‡Dorval, Eod. loco.
§Brera, Eod. loco.

of the iodide of potassium, make their appearance also in many persons, under the most diverse conditions of its internal administration as regards the dose of the drug and the duration of its continuance, with this distinction that there is a greater variety in the eruptions thus caused. The especial untoward action of the iodide of potassium has been known since the drug was first introduced into the materia medica, and innumerable references to it are contained in literature. As a general result the fact is established that the iodide of potassium may often produce cutaneous eruptions, with or without fever, from the simple erythematous to the petechial form, which may occur either alone or accompanied by other abnormal effects of iodine and which disappear, as a rule, soon after the suspension of the drug.

These eruptions are divisible, according to Fischer,* into four principal forms.

I. *The Erythematous Form.*—The skin, especially that of the forearms, but also of the face, is diffusely reddened or in circumscribed spots, and its temperature is elevated. With the discontinuance of the drug this symptom disappears after a few hours, but under its continued use the exanthem may develop into the most common form, viz.:

II. *The Urticaria-like Form.*—This occurs especially on the lower part of the trunk and extremities, but also on the other parts of the body. It appears as intensely red wheals which are slightly elevated, surrounded by an areola and gathered in groups, differing from true urticaria only in their higher color, being commonly described as of a pink-red color and turning pale under pressure. They disappear, without desquamation, on the discontinuance of the iodine.

III. *The Nodulo-pustular Form.*—This form is seldom observed, occurring most frequently in scrofulous subjects and usually on the upper part of the body. A deep-red, pruritic spot is formed, and is transformed through exudation into a papule or a bluish-red nodule, with or without an areola. This may persist, but as a rule, a colored vesicle filled with a clear fluid, or a pustule, which may either break or dry up, is developed on the top of it while the papule slowly disappears with desquamation after discon-

*Fischer, Wien. Medic. Wochenschr., 1859, No. 29, p. 470.

tinuing the use of the iodide of potassium, often leaving behind a bluish-red or marble-colored pigmentation of the skin.

As intermediate forms small blisters, acne-like pustules (iodine acne) and even furuncles are observed. Thus Brshesinsky* saw large furuncles surrounded by severe inflammation develop on the breast and between the shoulder blades in the case of a woman who took thirty drops of the tincture of iodine three times a day. Under the application of warm fomentations these furuncles fell off as nodes, leaving large ulcers behind.

IV. *The Eczematous Form.*—This is a very rare variety, and attacks chiefly the hairy scalp, and in the neighborhood of the scrotum. The differential diagnosis between this and syphilitic eruptions is not difficult, particularly as the form disappears very quickly on discontinuance of the drug.

For the sake of completeness a form more recently observed may be added :

V. *The Petechial Form.*—Fournier† describes this form, which he calls purpura jodina (Jodisme pétechiale), as a very rare affection. He noticed that the eruption, which has also been mentioned by Ricord, occurs during the first three days of the exhibition of the iodide of potassium, less frequently between the third and the sixth day. In some cases it appeared simultaneously with the exhibition of iodine, and in one patient a new eruption appeared with each increase of the dose. It was confined in each to the legs, (occurring only once in the trunk), and appeared more profusely on the extensor than on the flexor surfaces. It never appeared on the knees or on the feet. Usually as many as a hundred discrete patches occur on each leg. The eruption is miliary, the spots being mostly of the size of a pin's head, seldom reaching that of a lentil, and accompanied by no constitutional disturbance. It attains its perfect development within two or three days, and continues at the longest for from two to three weeks, when it disappears. Petitjean‡ confirms these reports in the main, but describes a case in which the eruption appeared also on the dorsal surface of the foot.

Auspitz § also observed a similar eruption in a patient who had

*Brshesinsky, Canstatt's Jahresber. f. d. ges. Medicin, 1843, iv., p. 32.

†Fournier, Revue Mens. de Medecine, 1877, p. 653.—Vierteljahrschr. f. Dermatologie u. Syphilis. 1878, p. 294.

‡Petitjean, l. c , p. 35.

§Auspitz, Vierteljahrsch f. Dermatolog. u. Syphilis, 1878, p. 204.

taken 25 pills of iodide of potassium of 0.2 gramme (gr. iij) each, or a total quantity of 5.0 grammes (gr. lxxv).

The occurrence of the untoward effects of the potassic iodide finds its most satisfactory explanation in the hypothesis that the drug, or the products of its decomposition, exerts a direct influence through the circulation on the respective parts. The theory of "the saturation of the system with the iodide of potassium," of which the symptoms detailed were regarded as the expression, and which was formerly accepted by most of the authors, is manifestly obscure and indefinite, and is so plainly refuted by the fact that these symptoms appear after even very small doses, that any further discussion of it may be dispensed with. In addition to this chemical analysis points also to the local origin of the affection.

It has long been known that iodine may be detected in the secretions, as the urine, saliva, sweat, milk and tears, shortly after the exhibition of the iodide of potassium. Adamkiewicz* assigns the cause of the iodine acne to the influence of the iodide on the sebaceous glands. According to this author the ingested iodide combining with the nitrate of ammonia present in the stagnant secretions of the skin, sets free the iodine, which may act as an irritant on the glands and the tissue adjacent and in this manner give rise to the affection. That the iodine eliminated with the sweat does not cause this affection is evident from the well-known fact that iodine acne does not attack the palms of the hands or the soles of the feet. Buchheim declares that the iodine eruption is due to the action of ozone on the iodide of potassium eliminated with the perspiration, the iodine being thus set free. That the drug selects these unwonted avenues of escape instead of being eliminated through the ordinary channels may be particularly due to individual peculiarities, or partially also to the fact that the urinary apparatus may be functionally less active, the inactivity, however, being still within physiological limits, as in the summer for instance, or it may be actually diseased.

Johnson† observed the appearance of a pustular iodine exanthem in many cases of Bright's disease as a result of small doses of iodide of potassium, and Rose‡ was able to detect iodine in the matter

*Adamkiewicz, Charité Annalen, iii., 1876.
†Johnson, British Medical Journal, Jan., 1859.
‡Rose, Virchow's Archiv, Bd. 35, 1864, p. 32.

vomited shortly after the injection of preparations of iodine into an ovarian cyst. In the latter instance the drug found its way into the stomach probably on account of a partial suppression of the urinary secretion.

The observation of Simon and Regnard (l. c.) that albuminuria is sometimes caused by an external application of iodine, shows that the drug may exert a direct influence upon the urinary passages. The potassic iodide is said to have a similar effect on some persons. Rodet (l. c.) and Petitjean (l. c.) report cases in which vesical tenesmus, dysuria, retention of the urine, and even hæmaturia followed the employment of this salt.

The old and common experience that iodine effects a reduction of hyperplastic glandular tissue, finds a physiological counterpart in the effect of the prolonged employment of medicinal doses of the iodide of potassium on the testicles, ovaries and mammæ. Many authors claim to have observed, under such conditions, various degrees of atrophy of organs, which were previously in a normal condition. It is probable that the direct localized action of the iodide, or the iodine in its composition, plays an important part in the causation of these effects.

As regards the genital system, an increased excitability of the sexual appetite, spermatorrhœa, and, in women, a greater profusion of the menses, are said not infrequently to follow the protracted employment of the iodide of potassium.

Mention must lastly be made of the disturbances of the general nervous system and of nutrition—that group of symptoms called by Rilliet "constitutional iodism," which follow, in many persons, the employment of iodine. According to this author, even minimal doses of the iodide of potassium, if long continued, are capable of producing this condition. The patients present a peculiar cachectic discoloration of the skin, and, in spite of the fact that the appetite is usually good, there may be considerable emaciation. This emaciation is apparent in the face, around the hips, breast and testicles, and is accompanied by a sensation of faintness and bodily weakness. In addition to these a series of nervous disturbances may supervene, as anxiety, restlessness, a kind of oppression called by French authors "ivresse iodique," disturbances of hearing, lancinating pains in the extremities, a slight jerking of the tendons, and nervous palpitation of the heart.

Though the facts thus far reported prove that the iodide of potassium often fails of its normal effects, causing in their stead untoward effects in the most varied organs, it would nevertheless be carrying the objection to its use too far to limit its use to but a few affections, as proposed by Rodet, inasmuch as these phenomena occur in only a limited number of cases, and are, in the main, of a transitory nature.

This fact does not, however, remove the necessity for caution in the administration of the iodide of potassium, and, especially in diseases of the throat and kidneys, and the suspension of the drug on the appearance of the first symptoms of untoward effects. Should disturbances of the intestinal tract, as vomiting, diarrhœa, etc., supervene immediately or in a short time after the exhibition of the drug, it would be well to examine the solution of the iodide of potassium with reference to its purity, for which purpose muriatic or sulphuric acid should be added to it. In the presence of the iodate of potassium a reduction takes place and iodine is set free.

BROMINUM.

Owing to the unpleasant physical properties of bromine the drug has not met with much favor as a therapeutic agent. It is, however, sometimes employed in aqueous solution in inhalations, and also in gargles, in infectious diseases. In addition to this it may be employed in the purification of dwelling apartments which are suspected of being infected. Recently the method devised by Frank, viz., the incorporation of the bromine in a solid substance has been resorted to. Pieces or sticks of infusorial earth, a very porous substance, capable of absorbing a large quantity of fluid, and of low specific gravity, are impregnated with liquid bromine. It requires seven times its volume of bromine to completely saturate it, and when placed in an air-tight vessel the saturation is preserved. The pieces are so dry as to permit of their being handled with the naked hand. In the presence of atmospheric air this porous substance gives off the bromine completely, in the form of vapor. According to Wernich* the entire cubic contents of a room may be rendered innocuous as regards the disease germs which it may contain, by evaporating in it 4 grammes (℥j) of bromine, after the

*Wernich Centralbl. für die Médic. Wissens.h. No. 11, 1882.

manner indicated, for each cubic meter (1¼ cubic yards) of the contents of the room. Owing to the great weight of bromine vapor—it being five-and-a-half times as heavy as atmospheric air—and the facility with which it is condensed, it is especially adapted to the disinfection of spaces which are difficult of access, as for instance, the holds of ships, casemates, vaults, etc. This method is certainly to be preferred to all others when it is possible to completely close up a room and prevent its use for a length of time. These conditions are necessary inasmuch as the bromine which in liquid form is a caustic to the skin and mucous membrane, is also an irritant when in the form of gas it comes in contact with the mucous membrane, exciting a condition which may vary from a slight degree of redness to one of violent inflammation. It is because of this property of the drug that one frequently observes conjunctivitis, coryza, salivation, a feeling of suffocation and slight bronchitis, with cough, in those who have inhaled bromine, either for therapeutic purposes or accidentally in rooms filled with its vapor.

The internal employment of bromine-water also frequently gives rise to catarrh, lachrymation, bronchial catarrh, salivation and diarrhœa. Glover,* in experiments on himself with this substance, observed only occasional gastric pains, though larger doses gave rise to nausea, a burning in the mouth, gastric oppression, etc. Other authors have shown by experiment that taken in small doses, for some time, bromine water exerts a depressing influence on the central nervous system, causing formication, a disposition to sleep, apathy, mental confusion, and a weakness of the reasoning power and memory. These symptoms disappeared on the suspension of the drug.

POTASSII BROMIDUM.

In contrast with the comparatively few and slight affections which arise from the use of bromine, may be placed a series of untoward effects following the internal employment of the bromides, and especially of the bromide of potassium, and what is true of this salt in this respect is also true of the sodium and ammonium salt. These effects evince in a general way a certain similarity to those

*Glover, Edinb. Medic. and Surg. Journal, 1842, p. 120.

caused by the iodide of potassium, but do not present such a variety, and when once developed are more persistent. The mucous membranes are more frequently attacked, though in a milder degree than by the iodide of potassium ; but, on the other hand, the effect in many cases on the integument, and more particularly on the central nervous system, exceeds in intensity and duration the effect of iodine.

The fact already noted of iodide of potassium, viz., that the occurrence of abnormal symptoms following its use is very much conditioned on the individuality of the person in whom they appear, is equally true of the bromide of potassium. For while these symptoms appear in many persons as a result of single or repeated small doses, there are others whose tolerance of the drug permits of their taking even poisonous quantities. As an illustration of this lack of susceptibility may be mentioned a characteristic case reported by Schweig,* in which 31 grammes (℥ j) of the bromide of potassium was taken in seven hours without the least manifestation of reaction, and 93 grammes (℥ iij) taken in the course of 48 hours caused only a diminution in the quantity of urine excreted, salivation and sleep. Arthand reports also fourteen cases in which the daily exhibition of from 10 to 12 grammes (ʒ ijss to ʒ iij) caused no cutaneous disease.

In a short time after its administration the bromide of potassium gives rise to a salty, and, according to some, bitter aftertaste ; sometimes there is also an increased secretion of saliva, traceable to an irritation of the mucous membrane of the mouth, and a reflex action on the salivary glands. In sensitive persons it causes a burning sensation in the throat, and sometimes a slight nausea and eructation, and when given on an empty stomach it occasionally causes pain in that organ, or a feeling of gastric oppression, warmth or fullness. Actual gastric catarrh following its employment is a rare occurrence unless the drug is given improperly or on an empty stomach. Occasionally eructation and vomiting are observed in some patients shortly after a dose of the drug; diarrhœa seldom occurs. On the other hand, as was first pointed out by Hütte,† the prolonged use of small doses, or larger quantities taken for a shorter time, occasions a blunting of the sensibility as well as of the reflex action of the soft palate, the root of the tongue, and the posterior wall of

*Schweig, Virchow-Hirsch's Jahresber, 1876, p. 401.
†Hütte, Gazette Médicale de Paris, 1850, Juin 28.

the pharynx. Gatumeau* noticed such complete analgesia after 3 grammes (gr. xlv) of the drug that irritation of the pharynx and epiglottis and of the posterior wall of the pharynx excited no reflex efforts at deglutition. Krosz† noticed on himself after large doses of the bromide of potassium such a diminution of reflex excitability in the parts indicated, that it was impossible to evoke reflex nausea by irritating the palate. The depression of the sensibility of the respiratory mucous membrane is not less marked. This fact must be borne in mind in connection with the bronchial catarrh with profuse secretion which not infrequently attends the prolonged employment of this drug, particularly in the treatment of epilepsy, mania, etc, Stillé‡ pointed out the possibility of the occurrence of dangerous and even fatal catarrh in the course of the prolonged employment of the bromide of potassium, through the prevention, by the diminution of the reflex excitability of the respiratory tract, of the fits of coughing which may be necessary to remove accumulated mucus. As Höring § found to be the fact in his own case, the bronchial catarrh is sometimes attended with pain in the larynx, paroxysms of coughing and hoarseness. According to older authors‖ hæmoptysis, which, however, disappears on the suspension of the drug, is said to occur in many who are subjected to its influence. No confirmation of this statement is, however, to be found in recent literature. As more recently remarked by Veiel,** a concomitant symptom to those mentioned, of the effects of the potassic bromide, is a fœtid odor of the breath. This cannot be due, as in the case of mercury, to any morbid changes in the mouth, inasmuch as the changes in the mouth wrought by this salt are insufficient. It is probable that the bromine in the salt suffers a temporary separation from the potassium in the body and that it is partially eliminated through the lungs, thus imparting the odor to the breath. It must not be inferred from this, however, that it is the bromine, as such, which excites the catarrhal changes in the mucous membranes, for although a small per centage of it may escape from

*Gatumeau, Thêse Montpellier, 1869.

†Krosz, Archiv für experiment. Pathologie u. Pharmacologie, Bd. vi, p. 15.

‡Stillé, Virchow-Hirsch's Jahresber. 1878, i., p. 384.

§Höring Ueber die Wirkung des Broms und seiner Präparate auf den thierischen Organismus, Tübingen, 1838.

‖Canstatt's Jahresbericht für die ges. Medicin, 1843, IV., p. 31.

**Veiel, Vierteljahrschr. f. Dermatol. u. Syphil., 1875, p. 17.

the body in the form of a vapor, the greater part immediately on its separation from the potassium finds a sufficiency of the metallic alkalies to enable it to exert its action on the various mucous membranes in the form of a bromide.

Among the mucous membranes which may be attacked are those of the nose and eyes, as is evidenced by the occasional occurrence of coryza, conjunctivitis, lachrymation, etc., as a result of the employment of the bromide of potassium. The functions of the visual apparatus are but slightly affected. Dilatation of the pupil is an almost constant effect of repeated doses of the bromide of potassium. Laborde* observed in several cases, within one or two hours after the exhibition of the drug, cloudiness of vision, and in some instances anæsthesia of the scleral conjunctiva. Hütte (l. c.) declared that myopia, amblyopia, and diplopia may be caused by the drug. Martin Damourette and Pelvet† affirm the latter fact, while Nicol and Mossop are said to have observed, in addition to this, dilatation of the retinal blood vessels. In opposition to these claims may be placed the experiments of Krosz‡ on himself and others, which always gave negative results as regards these pathological symptoms.

The bromide of potassium has been demonstrated to be capable of causing a wide range of affections of the genito-urinary organs. In addition to a positive increase in the secretion of urine, there is in some persons dysuria, a constant feeling of fullness of the bladder and a diminution of the sensibility of the urethral and vaginal mucous membranes. Rabuteau § declares that the prolonged use of the drug causes a diminution of the sexual appetite. Thielmann‖ had previously utilized this property of the drug by prescribing it as an antaphrodisiac, in doses of 0.18 gramme (gr. iij). Laborde (l. c.) on the contrary declares that he found it in his own case, and after a single large dose, to cause sexual excitement, erections and pollutions. Voisin** reports the same effect as occurring, though rarely, as a result of ordinary doses. A diminution of the catamenia is said to occasionally occur in women.

*Laborde, Gazette Médicale de Paris, 1869.
†M. Damourette et Pelvet, Bullet. de Thérapie, lxxiii., 1867, p. 241.
‡Krosz, l. c, p. 21.
§Rabuteau, Gazette Médicale de Paris, 1869, p. 312.
‖Thielmann, Medicin. Zeitung f. Russland, 1854.
**Voisin, Bulletin Générale de Thérapeutique, LXXXIII, 1867, p. 241.

The irritating action of the bromide of potassium on the skin denuded of its epithelium, and on the mucous membrane, manifests itself also in the frequent occurrence, in many cases, of a variety of cutaneous eruptions after its internal administration. These have long been recognized, and have been collectively designated as "bromine acne," although they belong to a different classification in dermatology.

Berenguier* observed them as occurring in fifty-three per cent. of all cases treated by the bromide of potassium, Clark and Amory† in sixty-six per cent., and Voisin in seventy-five per cent. Several authors, as Bedford Brown,‡ noted their occurrence accompanied by local or general elevation of temperature, while Veiel (l. c.) emphasizes the fact of the gradual and non-febrile occurrence of the acne-like efflorescence; Voisin observed the occurrence of fever in only one case of general bromine acne. Falret§ declares that he has always observed the occurrence of an eruption after the exhibition of 4 grammes (ʒ j) of the salt. It is, however, an established fact that it may be developed after much smaller doses. Children are, as a rule, more liable to be attacked by it.

The bromine eruptions which present themselves are differently described by different authors. They are, however, for the great part traceable to morbid changes in the sebaceous glands and their results, and since the different stages of the development of these affections are present at the same time—in the progressive and retrogressive metamorphosis of the affection—in one and the same person, they closely resemble the various dermatoses.

Voisin (l. c.) has classified all the changes of the skin which occur as a result of the use of bromine. But in view of other and more recent observations his classification may be advantageously increased to make room for the addition of several varieties. The following may, therefore, be regarded as embracing all the changes of the skin due to this cause. There appear, during the internal administration of bromide of potassium in certain persons, according to their specific predisposition and independently of sex and the systemic condition as regards health, at various times and after the most various doses, various affections of the skin, as:

*Berenguier, Des éruptions provoquées par l'ingestion des Médicaments, Paris, 1874, p. 4.
†Clark u. Amory, Virchow-Hirsch's Jahresber., 1872.
‡Bedford Brown, Virchow-Hirsch's Jahresber., 1873, p. 358.
§Falret, Annales Medico-psychologiques, 1871.

1. *The Erythematous Form.* This was regarded by Veiel (l. c.) as the sole untoward symptom of the action of the drug; and he maintained that it was attended by fever and occurred only on the lower extremities over which it was diffusely spread. The eruption was very painful. Brown (l. c.) also describes this form of eruption as an expression of the action of the bromide of potassium. He saw the development of rubeola in children under similar conditions.

2. *Acne.*—This is by far the most common form of eruption following the exhibition of the bromide of potassium. According to Veiel a thickened skin, which owing to the secretion of sebum has an unctuous feel, or an integument on which there are comedones or pre-existing acne, is peculiarly predisposed to the occurrence of this form of eruption. It appears, under various modifications, which present a complete analogy, as regards their seat and appearance, to ordinary acne. The first step in its development is generally an erythematous change in the skin, attended by a pricking and burning sensation. It is convenient to make a subdivision of this form into two varieties:

a. Acne Punctata.—This usually precedes the pustular form. It is characterized by the appearance of red elevations of the size of millet seed or peas, on a more or less indurated base with an areola, and attacks by preference the face, eyebows, hairy portion of the scalp, being more rarely situated in the breast and back, and almost never on the lower extremities. Veiel found that most of the nodules were pierced by hairs. After a longer or shorter duration this form may disappear with desquamation, or pass into

b. Acne Pustulosa.—This may be regarded either as a disintegration of the nodules or as an independent variety. The pustules are at first of the size of a pin's head, of a yellowish-white color, surrounded by an areola, becoming larger later on, and, according to Voisin, assuming even the form of ecthyma pustules. After a few days or weeks the pustule discharges its contents, and there remains in its place a solid nodule or a red spot. The number of these pustules varies. The whole face is occasionally covered and disfigured by the densely disposed points of efflorescence. The pustules persist from days to months, and should the drug not be discontinued they may persist for years. Ordinarily they disappear in from one to three weeks after the drug has been suspended.

Voisin (l. c.) noticed also that the number of the pustules was increased and diminished with the increase and diminution of the quantity of the bromide taken. After healing they frequently leave behind slightly depressed, irregularly round cicatrices or red spots. This pustular variety selects the same location for its appearance as does the papular variety above considered. In some cases the pustules become confluent, and on the scalp they are usually covered with crusts. Veiel examined the pus of the acne with negative results for bromine, being able to discover it only in the urine. Guttmann,* on the contrary, was able to demonstrate the presence of bromine in the secretion of the pustules in a man in whom pustular acne had supervened on the employment of the potassic bromide for a year, the drug at first having been given in quantities of 4 grammes (℥ j) a day, and afterward increased to 12 grammes (℥ iij). His method was the usual one, of separating the bromine from the potassium by added chlorine water to the diluted and filtered pus, and then extracting the bromine by means of chloroform.

3. *The Urticarious Form.*—This variety was several times observed by Veiel. It appeared only on the lower extremities, and on erythematous surfaces, in the form of wheal-like elevations of from a quarter to a half inch in diameter, very sensitive, and changed by degrees into a wart-like excrescence which went on to ulceration. The ulcer thus formed was deep and ill-conditioned, and disappeared as soon as the bromide was discontinued. This variety is, doubtless, identical with the tumor-like variety described by Voisin, which, according to this description, is of the form of oval-shaped tumors or elevations, from 2 to 5 ctm. (a half an inch to two inches) in diameter, of a rose or cherry color, with indurated base. They appear exclusively on the lower extremities, and particularly on the calves of the legs, and are covered with small yellowish prominences, which, on closer examination prove to be agminated, acne-like pustules, from which cream-like contents exude, either spontaneously or on puncture. They are very painful when touched, and may, should the drug not be discontinued, be changed into foul, atonic ulcers, which may continue for from three to four months, but which disappear in two or three days after the suspension of the bromide of potassium treatment.

*Guttmann, Virchow's Archiv., Bd. 74, p. 540.

Neumann* noticed a similar affection. He established the fact that these tumors are caused by an inflammation of the glands of the skin, accompanied by an increase of their cellular elements, and a consecutive hypertrophy of the cells in the cutaneous tissue, besides also an enlargement of the papillæ of the skin. The hair follicles are enlarged, and assume the form of long tubes or globular sacs, filled with pus, epithelial cells and masses of smegna.

4. *Erythema Nodosum.*—In two out of ninety-six cases treated with the bromide of potassium, Voisin observed, on the upper and lower extremities as also on the trunk, slightly elevated patches of different forms, some with smooth margins, and some with irregular outlines. They were from 4 mm. (one-fifth inch) to 6 ctm. (two inches) in diameter, of a dark red color in the centre, and lighter toward the periphery. They arise and disappear very quickly, and, as regards form, color and induration of the base, they are identical with erythema nodosum; while in their reappearance after being rubbed they resemble urticaria.

Veiel reports his observation of such cases of erythema nodosum, but that it was always confined to the lower extremities. Smith† saw also after larger doses of the bromide of potassium, large, slightly elevated patches of the size of a fifty-cent piece, of a purplish color, and having their seat on both arms. They bled very readily, were of an indolent character, and disappeared after the discontinuance of the drug.

5. *The Vesicular Form.*—Voisin observed in a single case the appearance of a weeping eczema on the thighs after the bromide of potassium had been administered for over a year. The observation stands unsupported in the literature of the subject.

6. *The Furuncular Form.*—The coincidence of the occurrence of furuncles with the employment of the bromide of potassium, has been noted by so many authors that there can be no doubt that the two stand in the relation of effect and cause. Voisin, Smith and Neumann observed the furuncles in various degrees of development and on different parts of the body. The latter of these observers saw them on the hairy portions of the face, and on the forehead and neck.

It must be mentioned in conclusion that Veiel (l. c) noticed

*Neumann, Wiener Medic. Wochenschr, 1878, p. 124.
†Smith, Virchow-Hirsch's Jahresbericht, 1879, p. 384.

the appearance of numerous warts on the face and legs of a lad, in a short time after he had commenced the use of the bromide of potassium.

There is a variety of opinion as to the manner in which the various affections of the skin which have been described, occur after the employment of the bromine salt. While Clarke and Amory regard the bromine acne as a trophic neurosis, and not as dependent on the elimination of the bromide of potassium, and while Veiel also, having failed to discover any bromine in the acne pustules, does not regard the eruption as due to a local irritation of the sebaceous glands, Martin, Damourette and Pelvet attribute the cause of the affection to the action of the drug on the skin, through which channel it is eliminated. The fact that Guttmann demonstrated the presence of the potassic bromide in the contents of acne pustules changes the *a priori* probability that the salt may be eliminated through the skin into a certainty. We find in this fact, on the one hand, an analogy established between similar eruptions excited by the iodine salts, and on the other hand, a confirmation of the view that it is the bromine and not the potassium of the salt, as has been declared by some authors, which is the cause of the disturbance. In support of this assertion the fact may be adduced that other combinations of bromine are followed by a similar effect. Thus Gowers* showed that similar eruptions follow the use of the bromide of ammonium, and Stark† reports that in seventy-five per cent. of all the cases of epilepsy treated with the bromide of sodium acne appeared, and that it was of longer duration and much more frequently went on to suppuration. In no instance did he observe an affection of the skin as a result of the administration of the chlorate of potassium.

The leading indication in the treatment of these affections is the suspension of the drug. Gowers (l. c.) employed Fowler's solution in the treatment of the acne. The daily administration of five drops of this preparation was sufficient to cause a disappearance of the acne pustules in fourteen days. That this result is due to the medicine is, however, simply imaginary, inasmuch as experience has shown that the affection may disappear within that time without a

*Gowers, Lancet, 1878, p. 866.

†Stark, Zeitschr. f. Psychiatrie xxxii., p. 1482.

resort to therapeutic measures. Prowse* employed for the same purpose a solution of one part of salicylic acid in thirty of water.

In contrast with the quite transitory untoward effects of the bromide of potassium which have heretofore been considered, we find a group of symptoms referable to a series of functional disturbances of the central and peripheral nervous system, which may be associated with the disturbances already described, which frequently continue after the suspension of the drug, and which leads to a permanent impairment of the health of the person affected. This condition is bromism, so-called.

Voisin makes a distinction between a chronic and an acute bromism and bromine-cachexia. There is usually a violent frontal headache in all forms of the affection, a symptom which is also occasionally observed as a result of the use of the bromide of potassium without the occurrence of bromism; a bronchial catarrh and a cough may also supervene as complications. Acute bromism may develop suddenly, even after years of tolerance of the potassic bromide and manifests itself in a staggering gait, mental apathy, lustreless eyes, somnolence, etc. While that form which developes slowly is characterized by a faded complexion, dryness of the mouth, a foul breath, emaciation, diarrhœa, a loss of the normal carriage of the body, trembling of the hands, weakness of memory and a loss of will power. It may, furthermore, manifest itself in symptoms referable to disturbance of the cerebro-spinal system, as delirium and hallucinations, and in disturbances of the centres of sensation and motion. According to Voisin (l. c.) the bromine cachexia sets in with loss of appetite, emaciation, and somnolence, and the resulting condition of weakness leads to the formation of carbuncles, and pneumonia, which may prove fatal, should the employment of the bromide of potassium be persevered in.

Though this classification is open to the objection of being too dogmatic, the fact is still established that all the symptoms which have been detailed may supervene, in the most varied modifications, on the employment of the bromide of potassium. The question as to which of the constituents of this salt these peculiar effects are attributable, has also been variously answered at different times. It

*Prowse, British Medical Journal, July 24, 1880.

may, however, now be accepted as a certainty that they are due to a combined action of the bromine and the potassium. Stark (l. c.) showed in his series of very careful observations that patients treated with the chlorate of potassium manifested symptoms of cerebral disturbance, such as confusion of ideas, a lessening of the reflex excitability of the pharynx, uncertainty of gait, etc. Krosz (l. c.) ascribes the cause of bromism to the bromine exclusively, in so far as it involves the cerebral and nervous elements, and charges the anæmia and motor disturbances to the potassium.

The treatment of bromism consists in a withdrawal of the drug, means for the acceleration of its elimination and an appropriate diet. The physical strength of the patient must be improved, and a change of residence must be advised as a means for the relief of the psychical symptoms. The kidneys are to be stimulated to facilitate the elimination of the bromide of potassium, inasmuch as they are the usual channels for the escape of the halogen salts; diuretics are, therefore, indicated.

POTASSII CHLORAS.

Jacobi* has more recently called attention to the dangers which may attend the exhibition of large doses of the chlorate of potassium, and has reported a number of observations of dangerous transitory symptoms and even fatal effects as resulting from such employment of it. These reports have been confirmed by the observations of Marchand,† Baginsky,‡ Hofmeier§ and Wegscheider.‖ On the basis of these facts Marchand declares that the chlorate of potassium should be entirely rejected in practice, and particularly in the treatment of children. It must be said, however, that the cases which he adduces in support of this declaration have been shown by Küster** not to be impervious to criticism in the matter of diagnosis. But should all drugs, which, when given in improper quantities, or even

*Jacobi, Gerhardt's Handbuch der Kinderkrankheiten, ii., p. 764 and The Medical Record, 1879, iii., 112.

†Marchand, Virchow's Archiv., Bd. 77, p. 456.

‡Baginsky, Arch. f. Kinderheilkunde, nach einen Vortrage vom 10 November, 1878.

§Hofmeier, Deutsche Medicin. Wochenschr., 1880, Nos. 38 and 39.

‖Wegscheider, eod. loc, No. 40.

**Küster, Berlin. Klin. Wochenschr., 1880, No. 40.

when given in their ordinary doses, occasionally give rise to unpleasant symptoms, be thus discarded, the materia medica would soon be reduced to the minimum of ingredients. In place of being thus ready to discard a drug, it would be well to first determine the exact doses suitable for different ages, and to determine as nearly as possible, the conditions of the system which perhaps predispose to those unpleasant symptoms.

The fact that over-doses of the chlorate of potassium are liable to cause fatal poisoning has been recognized ever since Lacombe* published a case of this nature. Isambert,† who employed the drug for several days, during which he increased the daily amount from 8 to 20 grammes (℥ ij to ℥ v), noticed as a result, greenish colored stools and increased discharge of urine, with accompanying pressure and pain in the region of the kidneys. He could detect the salt in the urine within ten minutes after its exhibition, and the elimination continued for one or two days. Podcopaen‡ demonstrated the poisonous action of the chlorate of potassium on dogs by injecting it subcutaneously.

The cases of poisoning reported by the authors cited present a series of symptoms rivalling in their definiteness and threatening nature those which follow the most active poisons. These symptoms are a continuous choking sensation and persistent vomiting, an icteric discoloration of the skin, pain in the stomach and in the region of the kidneys, epistaxis, diminution in the quantity of urine or anuria, which may last for a day or a day and a half, hæmaturia and albuminuria. These symptoms may be attended with insomnia, alternating sensations of cold and heat, without, however, demonstrable fever, a small, rapid pulse, violent hiccough, coma and death. In the case reported by Wegscheider there appeared on the seventh day of the poisoning an eruption of defined red spots, of the size of a bean, and not elevated, and becoming temporarily pale under pressure, at first confined to the arms and forehead but afterwards spreading over the entire body and becoming larger and of a copper color.

As opposed to these observations there may, however, be

*Lacombe, Journ. de Médecine de Bruxelles, 1856.

†Isambert, Etudes chimiques, physiologiques et cliniques sur l'emploi Thérap. de Clor. de Potasse, Paris, 1856.

‡Podcopaen, Virchow's Archiv. Bd. XXXIII. p. 505. 1865.

mentioned the fact that there had, previous to the record of them, been no case mentioned in the literature of the subject in which the exhibition of the chlorate of potassium, in medicinal doses, had been followed by other deleterious untoward effects than some disturbance of digestion. In speaking of medicinal doses we have in mind those given by Falck:* 0.1–0.5 gramme (gr. jss to gr. viij) per dose, or 5 grammes (gr. lxxv) during the course of the day, or those laid down by Jacobi (l. c.): for a child of from one to three years 1–2 grammes (gr. xv to gr. xxx) daily, and for adults 6–8 grammes (℥ jss to ℥ ij) a day.

It is, of course, understood that we eliminate from this connection those cases in which it is impossible to determine to a certainty whether the symptoms, or fatal issue, are due to the chlorate or to existing diphtheria for which the drug has been given. As soon as the amount of the drug exhibited exceeds the quantity ordinarily prescribed a list of deleterious effects may supervene, as Marchand has noted in his second observation: A boy of three or four years, who during the course of the day had taken 10 grammes (℥ ijss) of the chlorate of potassium for a stomatitis, became soporose, and was afterwards attacked with diarrhœa and vomiting. These symptoms were followed by delirium, epistaxis, hæmaturia and albuminuria, the urine also depositing a granular brownish sediment. It was fully two weeks before the normal condition was restored.

The treatment of such accidents can at best be but symptomatic. The stomach must be emptied of its poisonous contents, the vomiting allayed by pellets of ice, champagne, etc., and the kidneys soothed by means of demulcent drinks: these are the remedial measures to be resorted to.

POTASSIUM CHLORIDUM.

The chloride of potassium, regarded by Sander† as of equal value with the potassic bromide, is claimed by him to possess the advantage of not being followed in its exhibition by untoward effects. Neither of these statements have, however, been borne out

*Falck, Uebersicht der Normalgaben der Arzneimittel, Marburg, 1875, p. 10.
†Sander, Centralbl. f. d. Medicin. Wissenschaften. 1868, No. 52.

by further experiments. Thus Starck,* as has already been indicated, found that the chloride of potassium exerted no influence whatever in epileptic seizures, but that it, on the contrary, caused in individual cases a series of deleterious untoward effects similar to those aroused by the bromide given in medicinal quantities. These consisted of a slight degree of mental confusion, drowsiness, torpidity, pain in the limbs, diminished power of motion, difficulty of speech, lessening of the appetite, and in one case a complete suspension of the reflex irritability of the pharynx. During the manifestation of these symptoms the pulse diminished perceptibly in frequency.

POTASSIUM SULPHIDUM.

The external application of the alkaline sulphides, and particularly the sulphide of potassium, in the form of ointments, lotions and baths, may in certain persons, and particularly in such as are predisposed, not infrequently give rise to an irritation, the intensity of which is in indirect proportion to the quantity of the salt employed.

According to Bazin† there appears on a reddened base, and attended by intense pain, small, confluent vesicles, which become filled with purulent or serous fluid, and surrounded by an areola of two or three times the extent of their diameter. The affection disappears in the course of a few days.

But more serious symptoms may manifest themselves as a result of inunctions with the sulphide of potassium. Thus Bazin saw after four or five applications of a solution of 4 grammes (ʒ j) of this salt in 30 grammes (℥ j) of water, to the lumbar region, an intense phlegmonous inflammation, with the formation of pustules and abscesses. A peculiarity in this case was the fact that there was but a very moderate degree of inflammation on the thighs and buttocks, to which the lotion had also been applied.

*Starck, Zeitschr. f. Psychiatrie xxxii., p. 159.

†Bazin, Leçons sur les affections cutanées artificielles, Paris, 1862, p. 110.

EXCITANTS.

CAMPHORA.

Camphor taken into the mouth gives rise to a biting and afterwards burning taste, which is followed by a feeling of cold extending into the stomach. If kept for some time in the mouth it occasions symptoms of local irritation of the mucous membrane, pain, swelling, etc. The painful irritative action of the drug is also manifest when it is applied to abraded surfaces.

The effects noticeable after the internal exhibition of camphor in medicinal doses vary, according to Jörg,* with the individuality of the person affected. While 0.3—0.5 gramme (gr. v. to gr. viij.) occasions no perceptible abnormal sensation in some, from 0.03—0.06 gramme (gr. ss. to gr. j.) will give rise in others to headache, dizziness, slight mental confusion, flushing of the face, with dryness of the mouth and thirst.

The alcoholic solution of camphor is said to be more energetic in its action than the drug in substance. Purkinje† noticed in his own case after doses of upwards of 0.5 gramme (gr. vijss.) an agreeable excitement and enlivenment, resembling alcoholic intoxication, and a slight prickling sensation in the skin.

While these symptoms for the most part rapidly disappear, without any unpleasant sequelæ, the symptoms which follow enemata containing camphor are not infrequently more threatening and persistent, demanding therapeutic interference. In such cases there occur vomiting, the egesta smelling of the drug, strangury, heat, clammy perspiration, also having the odor of camphor, increased frequency of pulse, and exaltation of spirits which may even develop into delirium.

In such cases enemata of senna and sulphate of sodium, sinapisms to the nape of the neck and body, or cold compresses or cold douches to the head, are indicated by way of treatment.

*Jörg, Materialien zu einer Arzneimittellehre, Jena, 1827, p. 330.

†Purkinje, Neue Breslauer Samml., 1829, i., p. 428.

MOSCHUS.

The statements regarding the untoward effects following the use of musk are somewhat contradictory. Jörg* noticed in those on whom he experimented that doses of 0.06–0.25 gramme (gr. j to gr. jv) were followed by slight headache, particularly in the frontal region, mental confusion, dizziness and a sense of pressure in the eye sockets. As touching the digestive tract, Jörg, in his own case, experienced gastric oppression, eructations with a permeating odor of musk following 0.18 gramme (gr. iij) of the drug, and others noticed a burning and dryness of the throat. On the other hand Trousseau and Pidoux† experienced, after similar doses, only a peculiar warmth of the stomach and abdomen, which was followed by a pronounced sensation of hunger. Later they experienced also pain in the frontal and occipital regions, dizziness and an excitement of the sexual organs.

According to other observations of Mitscherlich‡ small doses of musk may occasionally give rise to vomiting without digestive disturbance, a peculiarity probably traceable to an inherent aversion to the drug. Diarrhœa has also been observed to follow the exhibition of musk.

RADIX VALERIANÆ.

The root of valerian, very generally regarded as comparatively inert, may, according to Jörg (l. c.), even in small doses, excite unpleasant symptoms in some persons. He occasionally observed the following symptoms, occurring either singly or combined, as effects of from 4 to 8 grammes (℥ j to ℥ ij) of an infusion of the root: a scraping sensation in the throat, eructation, nausea, headache, particularly in frontal and parietal regions; a feeling of constriction of the throat, borborygmi, diarrhœa, colicky pains and anorexia.

Barbier § noted hallucinations of sight in a person who was being treated with valerian.

*Jörg, l. c., p. 285.
†Trousseau et Pidoux, Traité de Thérap. IIIième edit, II., p. 193.
‡Mitscherlich, Lehrbuch der Arzneimittellehre, Berlin, 1849, Bd. II., p. 369.
§Barbier, Matière Medic. 1824, II., p. 83.

FLORES ARNICÆ—TINCTURA ARNICÆ.

Arnica, even in small doses and regardless of the manner of its employment, may cause disagreeable effects in some persons. An infusion of 0.3 to 1.0 gramme (gr. v to gr. xv) in 120 grammes (℥ jv) of water, not infrequently causes a burning and scratching sensation in the mouth and throat, pains in the stomach, eructations, a cutting pain in the abdomen, and occasionally also tenesmus and diarrhœa. Later an oppressive headache, mental confusion, dizziness and restless sleep ensue.

More recently Wilkinghoff* has shown that the active principle of arnica may become weaker and finally become inert with age. This fact offers an explanation of the diversity of action which attends the drug.

It appears that the symptoms mentioned as referable to the primæ viæ, are due to a local irritative action of the drug, and that the nervous disturbances are of a reflex nature. In support of this view may be adduced the fact that the application of the tincture of arnica to the sound skin, causes, according to the activity of the preparation employed, either itching and burning and shortly after a reddening of the affected parts, or miliary or linseed sized pustules, or even distinct bullæ, may appear on the reddened base. These changes are attended by decided constitutional symptoms.

*Wilkinghoff, Medicin. Beiträge zur Kenntniss der Arnica montana. Inaug.-Dissert. Bonn, 1880.

NARCOTICS.

OPIUM.

There is scarcely any other medicinal substance, the abnormal action of which is so largely dependent on the individual conditions of the patient, as is the case with opium. Among these conditions are the age and sex of the person, the nature of the disease, and, according to Charvet,* even the climate and race; in short, that peculiar susceptibility to the particular action of a certain drug, which is dependent on certain physical properties which it is difficult to define in a given case.

Regarding the matter of age it is to be noted that in many children deleterious and even fatal effects may readily follow the exhibition of opium. The recognition of this fact has caused it heretofore to be regarded as an axiom that opiates should be given in very small and definite doses in such cases. More recently, this teaching has been largely ignored, the dangers which have been said to result from the use of the drug being regarded either as overdrawn or absolutely without foundation. The numerous accidents, however, which are recorded in the literature of the subject, and in spite of small and even minimal doses of opium, serve as a good basis for this warning and argue for great circumspection in the employment of the drug. Thus Sobotka,† among others, reports several cases in which serious toxic symptoms supervened on the exhibition of almost minimal doses of opium and in one case even death ensued on the administration of a tablespoonful of a mixture of 180 grammes (℥ vj) containing 3 drops of laudanum and 15 grammes (℥ ss) of syrup of poppies. Edwards‡ and Smith § also, saw fatal effects follow even still smaller doses—0.0003 to 0.0006 gramme (gr. $_{2}\frac{1}{0\,0}$ to gr. $_{1}\frac{1}{0\,0}$). A larger number of similar observations have been collected by Taylor.‖

*Charvet, Die Wirkung des Opiums auf die Thier. Oeconomie. Leipzig, 1827.
†Sobotka, Journal f. Kinderkrankheiten, Decemb., 1845.
‡Edwards, Ref. bei Taylor die Gifte.
§Smith, Medical Times and Gazette, 1854, April 15, p. 386.
‖Taylor, Die Gifte, übersetzt von Seydeler, Cöln, 1863. Bd. III., p. 31.

Owing to their greater susceptibility to irritation women are, cæteris paribus, more apt than men to suffer from the abnormal action of the drug. Gastric disturbances and existing hyperæmia of the brain are, furthermore, conditions which predispose to these deleterious untoward effects. But constitutional bodily conditions are preëminently capable, in all persons, of modifying the normal action of opium or of exciting unwonted symptoms.

The untoward effects noted up to this time may manifest themselves regardless of the form in which the drug is given. They appear, however, to be most apt to occur after enemata, inasmuch as there are numerous cases on record, in which very minute doses of opium given in this form, were followed by threatening symptoms and even death. Whether, as maintained by Dupuytren,* absorption of opium is more rapid and complete from the intestines than from the stomach, thus facilitating a more complete action of the drug, has not yet been determined by experimentation.

We shall first consider the central nervous system as the seat of action of opium. There not infrequently occur in certain individuals after doses of 0.015 to 0.05 gramme (gr. $\frac{1}{4}$ to gr. $\frac{5}{6}$) intense mental confusion, vertigo and headache, lasting for several hours and even days, being sometimes referable to the frontal region and sometimes to the occipital. These symptoms were familiar to the ancient physicians, such as Scribonius, Largus and others. Tralles,† who reports an observation of this nature in a man, says regarding it in rather unclassical Latin: ". . . per multos dies ponderosissimum caput circumgestasse." Convulsions are also said to have been observed as an effect of medicinal doses of opium. Larger doses, which, however, fall short of the maximum amount, are furthermore asserted to have caused buzzing and ringing in the ears, confusion of ideas, dimness of vision, disturbances of hearing, and partial or complete unconsciousness. The motor tract may be affected in a similar manner, and, as stated by Albers‡, twitching of the tendons, particularly of the extensor muscles, tremor of the hands, jerking, a sort of paralytic weakness of the lower extremities and even temporary paralysis have been observed. Occurring either simultaneously with these symp-

*Dupuytren Leçons de Clinique Chirurgic. Paris, 1832, I. p. 187.

†Tralles, Usus Opii salubris et noxius, Vratislav, 1774.

‡Albers, Virchow's Archiv, Bd. 26, p. 225.

toms or independently of them, disturbances of the digestive apparatus may also present as effects of the action of opium. The mouth and the throat become dry, nausea and vomiting occur and the appetite fails. The latter, however, occurs most frequently only as a result of the repeated exhibition of the drug.

The changes which occasionally take place in the skin as a result of the use of opium, merit a special consideration. Aside from the very profuse diaphoresis which sometimes occurs, the face becomes turgid and highly reddened, while the rest of the integument is hot to the touch. In such cases tormenting itching without eruption may also occur. This "pruritus opii" was noted by Dioscorides,* Paulus Aegineta,† and other writers also in the last century, and described as an annoying and unbearable affection.

In rare cases an eruption occuring with or without itching has been observed to appear as a result of the medicinal use of opium. Tralles‡ was the first to describe this eruption. According to his view there exists a certain relation between it and the sweating which appears synchronously with it. The occurrence of sweating is however, not a condition of the occurrence of the eruption. Duclos § makes especial note of the fact that it may occur without diaphoresis.

The opium eruption generally occurs in the form of small red isolated spots, which resemble roseola in their general character. According to an observation made by Rieken ‖ these spots may spread over the whole body and thus present a scarlatiniform appearance. Even the mucous membrane of the mouth and throat may, according to him, be attacked with this "erythematous inflammation." He saw such an eruption in a man after each internal exhibition of opium, and even though it was merely employed in ointments and collyria containing it. These erythematous spots, according to Berenguier,** occur on the face, neck, arms and breast shortly after the exhibition of opium and disappear without leaving a trace behind. Behrend*** has also more recently observed an

*Dioscorides, De noxiis venenis. Cap. xxiii. Venetiis, 1516, p. 124.

†Paulus Aegineta, Opera. Lugduni, 1551. Lib. v. Cap. XLIII. p. 355.

‡Tralles, l. c. p. 137 und 138.

§Duclos, Journ. de Médec. Septembre, Novembre, 1846, Ref. in Schmidt's Jahrbücher, Bd. 64, 1849, p. 74.

‖Rieken, Schmidt's Jahrbücher, Bd. cvii., p. 22.

**Bereguiner, Des éruptions provoquées par l'ingestion des médicaments. Paris, 1874.

***Behrend, Berliner Klin. Wochenschrift, 1879, p. 626.

opium exanthem. This occurred after the exhibition of a powder composed of 0.015 gramme (gr. ¼) of opium and 0.5 gramme (gr. vijss) of sugar, and was attended by intolerable itching. On the chest it extended from the clavicles to the lower end of the sternum, and appeared also on the inner surface of the arms, on the flexor surfaces of the forearms and the wrists, on the thighs, from the location of the adductors to the popliteal spaces, and on the posterior and inner surfaces of the legs, terminating at the ankles in a stripe of livid discoloration of about three fingers in breadth. It appeared as a pale scarlatina-like red, which spread to the surrounding healthy skin, and was seen, on closer examination to consist of closely disposed papules of the size of a pin's head. Several days after the disappearance of the eruption a fine bran-like desquamation of the epidermis ensued.

Brand* also observed an eruption which occurred with intense itching and fever, and appeared on the trunk and flexor surfaces. It consisted of innumerable small points which gave it the appearance of diffused redness. In this case and in one of a similar nature, desquamation supervened after a week and continued for upwards of ten days, shedding flakes of various sizes.

The manner of the occurrence of this eruption is probably the same as that in which eruptions occur in connection with other medicines. We may in addition, in this case, regard as a cause, a direct action of the drug on the parts of the skin attacked or on the trophic nerves. This hypothesis enables us at least to form an opinion as to the most direct cause of this affection, even though we are unable to explain by means of it, how it is that only certain persons and only certain portions of the bodies of these are attacked. Notwithstanding the statement made by Behrend (l. c.) in his description of the case mentioned, that the occurrence of the opium eruption in consequence of a partial elimination of the drug through the skin, or even through its presence in the cutaneous vessels, is to be excluded "with absolute certainty," we cannot by any means so concede it, inasmuch as a similar elimination has been demonstrated and is known to occur in the case of other drugs. His claim that the eruptions following the use of opium and other drugs are due to a change induced by them in the blood, would, even were it true, be conditioned at least on a localized action of the dyscrasic blood on the skin.

*Brand, Berliner Klin. Wochenschr, 1879, p. 718.

In the matter of the treatment of the untoward effects of opium, the suspension of the drug is usually followed by a spontaneous recovery. Should very threatening symptoms, such as coma, etc., occur, external irritation, stimulants, ice compresses, cold baths, sinapisms, etc., are to be resorted to. According to Da Costa* the bromide of potassium is a preventive of the untoward effects of opium and particularly of the faintness, headache, dizziness and nausea, besides lessening also the pruritus of the skin, when taken in doses of 2 to 3.5 grammes (ʒ ss to ʒ j) several hours before the exhibition of the opium.

MORPHIA.

What has been declared of the action of opium is equally applicable to that of its most active constituent, morphia, and its salts. Headache, stupor and particularly nausea and vomiting—the appetite not being impaired—have been observed to follow its use. Thus Billroth† observed in the case of a lady that small doses—0.007 and even 0.003 gramme (gr $\frac{1}{9}$—gr $\frac{1}{20}$ were followed by such a feeling of anxiety, nausea and vomiting, that in spite of intense pain, she refused to take the drug.

Laborde accounts for the vomiting on the supposition that the morphia is of bad quality, having been partially transformed, by keeping, into apomorphia. There has, however, been no exact chemical investigation made on this subject. Bally‡ observed gastric pains occurring, especially in women, in addition to vomiting, as a result of the use of morphia. They disappeared simultaneously with the suspension of the drug. He also occasionally observed colicky pains referable to the region of the umbilicus. Brochin § has reported a case in which the "idiosyncrasy" against morphia was so great, that 0.0025 gramme (gr $\frac{1}{25}$) of the drug administered hypodermically caused irregularity of respiration, momentary suspension of the heart beat and profound narcosis.

Wernich‖ has called attention to the occurrence of paræsthesia of the sense of taste after the employment of morphine, which, ac-

*DaCosta, Virchow-Hirsch's Jahresbericht, 1871, I., p. 307.
†Billroth, Wiener Medicin. Wochenschrift 1868, p. 763.
‡Bally. Mém. de l'académ royale de Médic I. 99. 1828.
§Brochin, Gazette des Hôpit, 1877, p. 226.
‖Wernich, Archiv. f. Psychiatrie, Bd. II., p. 174.

cording to his observation, is particularly prone to supervene in patients who are much reduced, and in persons, otherwise healthy, who have suffered from prolonged inanition. These effects are probably due to a central excitation of a similar nature to that induced by santonin. The persons thus attacked complain, shortly after the injection, of an intensely bitter or sour taste, which, for the most part, ceases with the cessation of the action of the morphia.

The occasional untoward action of morphia on the eyes has been minutely described by v. Græfe.* It reveals itself, particularly in very irritable persons, in spasm of accommodation, which supervenes on the excitation wrought by the drug on the ciliary muscle. The focal point is brought so near that the range of accommodation is very much contracted, and myopia is the result. Sommerfrodt observed a spasm of accommodation, lasting only half a minute, to occur in an analogous manner after the subcutaneous administration of 0.01 gramme (gr. $\frac{1}{6}$) of morphia. The outlines of the faces and heads of those standing by the bed seemed to the patient to suddenly coalesce, so that he was unable to recognize any one. While, according to Græfe, this condition supervenes mostly in from half to three-quarters of an hour after the injection, it appeared in this case directly after it.

The use of morphia may also cause changes in the skin, as evidenced by the pruritus and exanthematous eruptions which follow. Thus Apolant† saw an urticaria-like eruption occur in a man who took several doses of twelve to fifteen drops of a solution of 0.08 grammes (gr. j$\frac{1}{3}$.) of muriate of morphia in 10.0 grammes (℥ ijss) of bitter almond water. The patient, without knowing the ingredients of the prescription, attributed the eruption to morphia, from the fact that he had observed his susceptibility to this untoward effect of the drug on a previous occasion. The eyelids became swollen, the whole face œdematous, and the hands and other parts of the body covered with red, wheal-like elevations. Desquamation set in after five days, following which whole pieces of epidermis could be pulled off.

The peculiar untoward effects of morphia mentioned are to be distinguished from the symptoms which certainly and frequently occur, although the manner of the occurrence is not clear, after the subcutaneous injection of the drug when the canula is accidentally

*v. Græfe, Archiv f. Ophthalmologie, Bd. IX., 2, p. 62.
†Apolant, Berliner Klin. Wochenschrift 1877, p. 361.

introduced into a vein, thus making a direct intravenous injection. Under such circumstances there occur, as Chouppe* has stated, flushing of the face, heaviness of the head, confusion of ideas, increased frequency of the pulse, up to 100 beats, a feeling of anxiety and cold perspiration. These symptoms disappear in a few minutes, and may be prevented by a slight withdrawal of the canula after it has been introduced, or by first introducing the canula, and injecting the fluid only after any bleeding which may occur from the puncture has ceased.

Disagreeable effects have quite frequently been observed when opaque solutions of morphia, due to fungi, have been used for subcutaneous injections. Thus Dumas† reports a case in which, after the injection of the opaque precipitate of a solution of morphia, a phlegmonous erysipelas of the abdominal walls was developed. At the site of the injection there was a hard nucleus which soon developed into an intensely red swelling, which included almost the fourth part of the abdomen. A putrid liquid was evacuated by incision. There appeared inflammation and scaly desquamation of the subcutaneous areolar tissue with violent symptoms. Under antiseptic treatment, and after several incisions had been made, the patient recovered. Dumas recommends the boiling of the solution before each injection.

According to the investigations of Hamberg‡ a solution of the sulphate of morphia keeps longer, and is less inclined to decomposition and to the formation of mycelia than a solution of the muriate of morphia.

As a conclusion to this subject we shall notice the pathological condition which has frequently and thoroughly been discussed in recent literature, as following the habitual use of opium or morphia.

OPIUM EATING AND THE MORPHIA HABIT.

The symptoms which develop as a result of the continuous employment of opium in increasing doses, are of the same nature as those which attend the internal or hypodermic exhibition of morphia. The quantities which can be taken by some persons for a long time

*Chouppe, Gazette hebdomd de Médecine et de Chirurg. Mars, 1876, p. 162.
†Dumas, Bullet. génér de Therap. 30 Juin, 1831.
‡Hamberg, Pharmaceut. Zeitung No. 49, 1881.

without injurious effect are enormous, when we recall the smallness of the dose ordinarily required to give rise to grave and even fatal symptoms. Were it not for the fact that we are obliged, through indubitable evidence, to believe the reports of the enormous amounts which are said to have been given, we should give the reports of such quantities but little credence. Toleration for doses, which, under other circumstances would certainly be fatal, is conditioned on habituation to the action of the poison, and can only be established by commencing with small doses and gradually increasing them. There is nothing to oppose the view that the cell groups whose functions are especially involved are at first only temporarily changed by the opium, then losing their energy through the continuous chemical or physical influence exerted on them, they demand an increasing strength in the irritant to arouse the same functional capacity which previously obtained, and are thus at the same time protected against the danger of poisonous action on the part of the drug given. Finally, however, a point must be reached at which the quantities given are no longer sufficient to arouse or to inhibit certain organic functions, and when a further increase of the dose induces such deep-seated changes in the organ itself, or, through reflex or sympathetic action in other organs, that the symptoms of poisoning and its consequences supervene.

These conditions may be developed through the repeated therapeutic employment of opium or morphia. The patient who has come to understand the anodyne effect of these drugs resorts to them when opportunity offers, for relief in conditions of such slight indisposition as would be borne by another without seeking medical aid. Herein lies the first step on the track which leads inevitably to the pernicious use of these narcotics. For when the unpleasant bodily conditions which furnish an excuse for the taking of the drug are wanting, there appear first, psychical emotions, as worry and anxiety, which are superseded by slight mental disturbances, anger, vexation, etc., happy forgetfulness to which, or a pleasant alienation of consciousness lasting for hours, is secured by suitable doses of the opiate. And should these inducements fail, the constantly increasing indisposition to work, the neglect of social and domestic duties, and the other manifold changes in the emotional nature as well as in the bodily functions, furnish an excuse for a further

increase of the dose, until a bodily and spiritual marasmus, or a natural or violent death closes the deplorable scene.

Before the more promptly and powerfully operative morphine came into the extensive employment which now obtains, the phases of the abuse of narcotics, above described, were observed either singly or collectively in the effects of opium. Flemming* gives a graphic description of the moral condition and bodily tortures of the opium eater. He shows how such persons can only be induced by strategy to acknowledge their vice, how they have become lost to all sense of shame, and how social and family ties are severed by this passion. In the advanced stages of this condition there are mental depression or exaltation, childish impatience, inability to think or to fix the attention on a certain object, a want of interest in the daily occurrences of life, as also a beclouding of the memory and judgment. Simultaneously with these, bodily sufferings manifest themselves, such as sleeplessness, a gnawing pain in the region of the stomach, anorexia, chilliness with sweating, and not infrequently disturbances of the sexual function.

Morphia taken internally gives rise to the same symptoms. In a case reported by Samter† the morphia habit was continued for three years, during which in a period of about 323 days, upwards of 79.5 grammes (℥ ij ss) were taken. Eder‡ reports still larger doses. In the case observed by him the patient took laudanum for six years in increasing doses up to 30 grammes (℥ j) per day, for eighteen months pure opium, commencing with 1 gramme (gr. xv) and increasing to 9 grammes (℥ ij¼), daily; and for eighteen months morphine in commencing quantities of 0.4 gramme (gr. vj), which were later increased to 2.6 gramme (℈ ij) a day.

The introduction of the hypodermic use of morphia and the practice of intrusting the syringe to the patient to be used either personally by himself or by his attendants, has undoubtedly done much to cause the spread of the morphine habit, although we are not yet quite justified in saying with Bouchardat,§ "que le morphinisme fait à Berlin de tels progrès qu'il y a des maisons de santé spéciales pour en recueillir les victimes."

*Flemming, British Medic. Journal, February 51, 1868, p. 177.
†Samter, Deutsche Klinik, 1864, 16, 17.
‡Eder, Oestreichische Zeitschrift f. pr. Heilkunde, 1864, No. 33.
§Bouchardat, Annuaire de Thérapeut. de Matière médic. Paris, 1879, p. 13.

Observations bearing on this subject have been of increasing frequency of late years. Mattison,* in America, has called attention to the abuse of morphia which obtains in that country. Lähr† and Fiedler‡ were the first to raise their voices against the spread of this vice in Germany, which they attributed in part to the medical profession. Coincidently with Fiedler, L. Lewin§ reported a case of the morphia habit. More recently Levinstein,‖ basing his remarks on extensive observations, has treated the subject most thoroughly, and following him Burkart** reported his observations.

In all cases there is an equal and gradual decline of the psychical life, and further a series of bodily ailments, such as we have indicated as pertaining to the action of opium and to the untoward effects of morphia. As less frequent symptoms there appear in some cases slight transient albuminuria and also glycosuria, in a similar manner to their occurrence in other conditions of chronic intoxication. The morphia habit should be regarded as such a condition, and we cannot share the opinion of those who regard either the individual groups of symptoms or the entirety of the pathological appearances which present, as diseases in themselves. For the arsenic habit, alcoholism, and the group of saturnine affections and other states in which the mental and bodily conditions are equally extensively affected, may be regarded, from a clinical standpoint, as intoxications which have only received such a special impress through the secondary phenomena due to the long continuance of the condition, as have made the pathological aspect somewhat complex.

The therapy of opium-eating and the morphia-habit consists, naturally, in the withdrawal of the drugs. Regarding the manner of this withdrawal, *i. e.*, whether it shall be sudden or gradual, there is a diversity of opinion. This question, as it applies to pure opium, was discussed before the morphia-habit was known. Christison first enforced the sudden withdrawal of the narcotic in 1850. According to Flemming (l. c.) the mental and bodily sufferings of the patient are aggravated by this method; he becomes sleepless, irritable,

*Mattison, Schmidt's Jahrbücher, 1875, No. 1, p. 21.
†Lähr, Zeitschrift f. Psychiatrie 1872, H. 3.
‡Fiedler, Deutsche Zeitschr. f. pr. Medicin 1874, No. 27.
§L. Lewin, Eod. loco 1874, No. 28.
‖Levinstein, Die Morphiumsucht, Berlin, 1876 und Berl. Klin. Wochenschrift 1875, No. 48.
**Burkart, Die chron. Morphium vergiftung, etc., Bonn, 1877.

anxious, despondent and begs and importunes for opium. In connection with this condition there are thirst, neuralgic pains, diarrhœa, sweats, chills, etc. But a sudden withdrawal of the drug tests the physical and moral powers of the patient less severely than a gradual diminution, for after each dose let it be ever so small, there is an unpleasant reaction. In recent times both methods have also been advocated for the withdrawal of morphia. In the course of withdrawal should the patient be perfectly isolated and have no opportunity of recourse to morphia, conditions of collapse are of quite frequent occurrence, and to combat this it is necessary to resort to analeptics, otherwise a fatal issue may easily ensue. The state of excitability which occurs shortly after the withdrawal of the morphia is equally to be feared, inasmuch as suicide in this condition is not an uncommon occurrence. The only means of determining whether morphia has been secretly administered during the period of withdrawal is furnished by a study of the subjective condition of the patient. Should this be very good there is in the fact room for suspicion. The demonstration of the alkaloid in the urine is generally an unreliable test, from the fact, as established by Landsberg,* that the drug is very readily decomposed in the blood.

Only a very small proportion of these patients succeed in really and permanently weaning themselves from the morphine. By far the largest number of them fall again into the old vice shortly after the withdrawal of the drug. The exhibition of substitutes for the morphia, such as cannabis indica, hyoscyamus, etc., has been attended by no results. So also is the use of atropia, valerianate of zinc, quinine and the bromide of potassium, as symptomatic remedies, not indicated, inasmuch as the temporary relief of one or another pathological condition, the cause not being removed, is quite useless.

CANNABIS INDICA.

EXTRACT CANNABIS INDICÆ.—TR. CANNABIS INDICÆ.

There occur, dependent on the strength of the preparation and the individuality of the patient, after the exhibition of the preparations of hemp, untoward effects of varying degrees of intensity, which

*Landsberg, Pflüger's Archiv, Bd. xxiii., 1880, p. 432.

differ from the symptoms following the use of opium in being of relatively rare occurrence, in being transitory in their action and in leaving no unpleasant sequelæ. The facts pertaining to this subject have been recorded by Schroff.* He usually observed in those on whom he experimented, a blunting of the sense of touch with a sensation in the lower extremities as if asleep, vertigo, visual delusions and slight delirium. Husemann† noticed as a result of an experiment on himself, an alarming state of hilarity, while on another occasion his spirits were depressed and sorrowful, a condition with which the hallucinations and illusions which he experienced were fully in keeping.

CAFFEINUM.

Caffeine, so largely employed as a remedy in migraine, seems to produce different effects in different persons. Husemann‡ noticed after only 0.24 gramme (gr. jv.) severe determination of blood to the head and embarrassment of respiration, while Albers§ experienced no result after 0.18—0.3 gramme (gr. iij—gr. v) of the citrate of caffeine. Frerichs, who took two grammes (gr. xxx.) of the pure caffeine, felt only a slight sensation of cerebral congestion and vomited but once.

FOLIA HYOSCYAMI.

EXTR. HYOSCYAMI.

The untoward effects following the employment of the preparations of hyoscyamus have very much in common with those excited by belladonna. The affections of the skin are particularly prominent, amounting in many persons to an erythema. Thus Cabot‖ reports the case of a man who took tr. hyoscyamus to relieve a pain in the abdomen. In a short time his nose began to swell, and a slight swelling, accompanied by itching and a burning sensation, spread over his whole body. The face became red and shining, and this redness spread to the line of the umbilicus, below which

*V. Schroff, Lehrbuch der Pharmakologie, 1855, p. 536.
†Husemann, Handbuch der Toxikologie, 1862, p. 430.
‡Husemann, l. c., p. 544.
§Albers, Deutsche Klinik, 1853, 34.
‖Cabot, American Journal of the Medical Sciences, October, 1851.

there appeared only separate red spots. This erythema began to fade in the course of an hour and a half, and almost entirely disappeared in a day. Bessières* observed in a lady who had frequently taken vaginal injections of a decoction of hyoscyamus, an erythema of the face after an enema of the same material. Picard† also reports the case of a woman in whom there occurred an erythema of the face after the use of enema containing a medicinal dose of hyoscyamus.

Golding‡ saw several occurrences of a pustular eruption following the internal exhibition of small doses of hyoscyamus.

Functional disturbances of other organs may occur simultaneously with this affection, such as excessive dilatation of the pupils, dizziness, weakness and collapse. Paralytic conditions of the upper and lower extremities have also occasionally been observed. The continued use of the drug is further said to give rise to swelling of the parotids, salivation and catarrh of the nasal mucous membrane.

Therapeutic measures are only demanded for the weakness which occurs, and consists in the exhibition of stimulants.

HYOSCYAMIN.

HYOSCIN.

The alkaloid of henbane has recently been introduced into psychiatry, for its simple sedative properties, its mode of administration being partially internally and partially hypodermically. The untoward effects of the drug have thus become more familiar than formerly. Some of these untoward effects may be due to the bad quality of the drug or to a defective preparation of it. But the purest, crystallized hyoscyamin may also, in some persons, give rise to them.

Empis § gave pills containing 0.005 gramme (gr. 1-12) of hyoscyamin to a patient who had previously employed large doses of hyoscyamus. The first dose excited a condition of irritability, the

*Bessières, Abeille Médicale, November, 1853.

†Picard, Ref. bei Fodéré, Traité de Médec. légale et d' hygiène publ. T. IV., p. 25.

‡Golding bei Wibmer, Wirkungen d. Arzneimittel und Gifte. München, 1842, Bd. III, p. 149.

§Empis, Gazette des Lôpit. 1879, p. 949.

patient (a female) becoming as if intoxicated, the blood rushing to her head, and vomiting supervening. The second pill, given the next day, caused a return of the uneasy symptoms, the speech became difficult and swallowing impossible, and a delirium, similar to that caused by alcohol, occurred; respiration became laborious, the pupils dilated and in addition to these there were symptoms of clonic convulsions. This condition lasted for three hours and demanded the exhibition of analeptics.

According to the observations of Reinhard,* also, the prolonged employment of hyoscyamin gives rise to undesirable symptoms. He administered to an insane person subcutaneous injections (0.05 gramme [gr. 5-6] in 5.0 gramme [ʒ j] of water), and observed as a result a decrease of nutrition, a sickly aspect, and frequently the occurrence of boils.

Hyoscin, the alkaloid prepared by Ladenburg from amorphous hyoscyamin, of which there is a crystallizable hydriodate, also gives rise, during its therapeutic employment, to untoward effects similar to those induced by atropia. Edlefsen and Illing,† and Gnauck‡ also, assert that there is great variability in the individual susceptibility to the drug. Some persons cannot tolerate even 0.0001 gramme (gr. 1-600) of hyoscin, while in others the subcutaneous injection of 0.0025 gramme (gr. 1-25) gives rise to no particularly untoward effects. Of the latter a feeling of oppression, and benumbed sensation, especially in the frontal region, of the head, and pressure over the eyes, were noticeable. Following these there is usually thirst, dryness of the throat, nausea, trembling, a sensation of heat and labored breathing. In addition to these there are also a sensation of dizziness, numbness, intoxication and a staggering gait. This condition may disappear in the course of an hour, leaving nothing beyond a disagreeable sensation in the head. Should the condition, however, be aggravated, there occurs a delirium of the nature of that caused by the use of atropia.

*Reinhard, Archiv f. Psychiatrie, XI., p. 391.

†Edlefsen u. Illing, Centralbl. f. die Med. Wissenschaft, 1881, No. 23.

‡Gnauck, Eod. loc. No. 45, 1881.

ATROPIA.

ATROPIÆ SULPHAS.

The external employment of normal doses of atropia in eye practice, is, in addition to its physiological mydriatic action, attended, in some persons, by abnormal local and general symptoms of its absorption.

As regards the local symptoms, Von Græfe* observed that the mydriatic, at first non-irritating, cannot be long borne by certain persons. There occurs, as a result of the repeated action of the drug, an anatomical change, which affects the normal susceptibility of the conjunctiva to the further influence of medicine. There thus occur blepharo-conjunctival irritation, lachrymation, œdema of the lids and even an erythematous eruption, after each fresh instillation of atropia, when the conjunctiva has once become saturated with the drug. This antipathy of the conjunctiva sometimes continues for months after the suspension of the drug, the mucous membrane the while being to all appearances perfectly normal. In some of the more developed cases there appears a peculiar form of granulations, resembling the usual vesicular lymph follicles of the lower lid and distinguishable from them by the consistency and yellowish color of their contents, and the diminished vascular supply of the mucous membrane. As a means of permitting the renewed employment of atropia, Græfe† recommends the intermittent use of solutions of the acetate of lead or the nitrate of silver.

Hiller‡ traces this "atropia-conjunctivitis" to the action of fungi, especially the thread-like fungi, which are very frequently formed in solutions of atropia.

According to the investigations of Krœmer, § who noticed almost typical irritation of the conjunctiva immediately after the instillation of a solution of atropia thus changed, such solution may be rendered perfectly clear, and kept so by boiling and the addition of boracic acid (4 parts to 100 of water) and carbolic acid (1 part to 1000 of water).

*A. V. Græfe. Archiv f. Ophthalmol., Bd. I, 2., p. 242 und Bd. X, 2, p. 200.
†Græfe, Eod. loco Bd. II.
‡Hiller, Zeitschr. f. Klin. Medic. Bd. iii, Heft 1.
§Krœmer, Correspondenzbl. f. schweiz. Aerzte, 1881, No. 19.

In addition to these local changes Græfe observed as a result of the use of atropine, particularly in syphilitic iritis, an occasional permanent dilatation of the pupil.

The symptoms of the absorption of atropia, following its application to the eye, point to an action of the drug on the central nervous system, such as otherwise occurs only as a result of poisoning by the drug. These are on the whole but very seldom observed either after instillation of the drug into the eye, or the use of eye washes containing it, and are not due to the amount absorbed from the eye, but rather to that which finds its way through the tear ducts into the throat and stomach. The susceptibility to atropia is, therefore, thus directly proportioned to the patency of the tear ducts. In evidence of this fact may be adduced the circumstance noted by R. Liebreich* that the prolonged use of collyria containing the largest doses, by patients suffering from impermeable tear-ducts, gives rise to no constitutional symptoms. According to observations by Chassaignac three or four drops of a solution of 0.06 gramme (gr. j) in 10 grammes (ʒ ijss) of water, instilled into the eye in a case of double cataract with adhesions of the iris to the lens capsule, caused dizziness in half an hour, and later turgescence of the face, a scratching sensation in the throat and mental hallucination, which disappeared, spontaneously, three or four days later. Laborde† saw it produce in adults mental confusion and delirium, while Galezowski noticed symptoms of convulsions only in children.

The statements of Laborde are corroborated in an interesting manner by the contribution by Kowalewski‡ of the report of a case in which a man into whose eye an unusually large quantity of atropia had been instilled, became very much excited, and experienced also hallucinations of sight, hearing and feeling, which hallucinations the patient described as the embodiment of abstract conceptions. On the fifth day there appeared also a dryness of the mouth, spasm of the pharynx, etc., from which it took ten days to completely recover.

An observation of von Græfe § merits especial mention, viz., that not unfrequently there occur as a result of the continued use of

*R. Liebreich, Berliner Klin. Wochenschrift, 1864, p. 457.
†Laborde, Gazette Médicale de Paris, 1878, p. 606.
‡Kowalewski, Allgemeine Zeitschr. f. Psychiatrie, Bd. 36. Heft 4.
§v. Græfe. Archiv f. Ophthalmologie, Bd. IX., 1864.

collyria of atropia, symptoms which may be regarded as of erethistic debility and suspension of assimilation. This is a condition which it is difficult to distinguish and to assign its true cause, owing to the absence of the other symptoms of the action of atropia.

An analogous condition to this is furnished by experiments which Rossbach and von Anrep conducted on dogs. The animals become habituated to the drug, but also become emaciated, debilitated, and lose their energy, spirits and appetite. In spite, however, of the habituation, each new dose of the drug causes acceleration of pulse and mydriasis.

It is not necessary to indicate curative measures for these affections, inasmuch as the symptoms detailed usually disappear shortly after the suspension of the drug. When they are unusually severe, small doses (0.005 to 0.01 gramme [gr. $\frac{1}{12}$ to $\frac{1}{6}$]) of morphia may be given, but prophylactic measures are to be preferred. According to R. Liebreich (l. c.), patients should be recommended to bend their heads forward during the instillation of the atropia, in order to prevent them from swallowing the tears or the solution which escape from the eyes, to frequently blow their nose, and to gargle or to press the eyelid so that the tear duct may be drawn downward. Inasmuch as this plan, owing to the recumbent position, awkwardness, etc., of the patient, does not always succeed, Liebreich seizes the edge of the lid with a pair of small pincers, of the nature of a serre-fine, so as to produce a certain degree of ectropion, thus directing the punctum lachrymale downwards and outwards. It is usually sufficient to only treat the lower lid in this manner, but when large doses are employed, or in the case of susceptible persons, the upper lid must be similarly treated.

The internal exhibition of atropia is less frequently followed by untoward effects. When such do appear they are usually confined to dryness of the mouth, a raw sensation in the throat, slight fullness of the head, the appearance of rings before the eyes, and sometimes also diplopia and flushing of the face. It is only as a result of large doses that threatening symptoms supervene, referable to the circulatory system, the motor and psychical spheres and sensations.

Occasionally after the use of small medicinal doses there arises an affection of the skin. Thus Lusanna* reports a case in which the

*Lusanna, L'Union Médicale, 1854.

skin presented an intensely red color, as if it had been exposed to the intense heat of the sun, in fifteen minutes after a small dose of atropia. This erythema lasted from half an hour to an hour, and appeared after each exhibition of the drug.

HOMATROPIN.

Homatropin, the product of the action of hydrochloric acid in atropin, was used both in this form and as the bromhydrate of homatropia, as a mydriatic and also as a remedy against night sweats of phthisis, by Bertheau* and Fronmüller.† Its general properties are similar to those of atropia, from which it differs, however, in that it requires larger quantities to cause poisonous effects and that these effects disappear more quickly.

The following untoward effects have been observed to occur as a result of the internal exhibition or subcutaneous introduction of 0.02—0.1 gramme (gr. $\frac{1}{3}$ to gr. jss) of this substance: weakness and uncertainty of gait, vertigo, a feeling of fatigue, irritation of the throat, difficulty of deglutition, excited babbling and fullness of the head.

BELLADONNA

FOLIA—RADIX—EXTRACTUM—UNGT.—BELLADONNÆ.

Various authors have noticed an eruption after the external and internal exhibition of belladonna, which, like most medicinal eruptions, is of a very transient nature. This skin affection is sometimes general and sometimes localized, and appears, according to Guerard,‡ even after small doses, especially in small children. It generally takes the form of extensive erythematous spots, or a scarlatinal exanthem. The spots disappear on pressure, but return when it is removed. They appear chiefly on the face and neck, are unattended by itching, and soon disappear. The eruption may appear very shortly after the exhibition of the drug and may pass through its several stages of development, from the most pronounced redness to paleness,

*Bertheau, Berl. Klin. Wochenschrift, 1880, No. 41.
†Fronmüller, Memorabilien, 1880, No. 7, und 1882 Heft I.
‡Guérard, Des éruptions médicamenteses pathogénétiques, Paris, 1862, p. 26.

in a few hours. In some cases, as if to complete the resemblance to scarlatina, there is also redness and pain in the throat. There is neither fever nor desquamation.

Traube* declares, from his own experience, that a similar exanthem may follow the use of belladonna. Berenguier† observed a diffuse scarlatinal redness following the use of a belladonna mixture, which lasted for eight hours and then suddenly disappeared.

Wilson‡ noticed the appearance of a sclarlatiniform exanthem which disappeared in the course of three or four days without desquamation, in two lying-in women, for the swelling of whose mammary glands he had used a belladonna liniment for several days. Köbner, also, found a noticeable hyperæmia, particularly on the face, after the employment of a vaginal suppository containing extract of belladonna.

Bader § observed grave symptoms as a result of the employment of a vaginal suppository compound of cacao butter, and containing 0.2 grammes (gr. iij) of extract of belladonna. In five hours the face of the patient became of a scarlet red color, with cold cheeks, pulse 160, cool surface, dilated pupils and irritation of the throat, the general condition, however, remaining unimpaired. These threatening symptoms rapidly disappeared under the use of a hypodermic injection of 0.03 gramme (gr. $\frac{1}{12}$) of morphia and the administration of champagne.

It follows, as a matter of course, that belladonna may also, through its internal and external exhibition, give rise to the abnormal somatic symptoms identical with those specified as following the employment of atropia. Two cases observed by Golden‖ in which the employment of belladonna ointment to the breast caused a suppression of the secretion of milk, are worthy of note in this connection.

DUBOISINUM.

Duboisia is a yellow alkaloid, in the form of an extract, procured from an Australian plant belonging to the solanaceæ, the

*Traube, Beiträge zur Pathologie und Physiologie, Berlin, 1871, II., Abth. 1 p. 163.
†Berenguier, l. c., p. 31.
‡Wilson, Virchow, Hirsch's Jahresbericht f. d. ges. Medicin, 1872, I., p. 380.
§Bader, Correspondenzbl. f. schweiz. Aerzte, 1 Octob., 1881.
‖Golden, Lancet, 1856, No. 6.

duboisia myoporoides. It was prepared by Gerrard and simultaneously by Petit, in 1878. It is slightly soluble (1:120) in water, but readily soluble in alcohol, chloroform, etc. The watery solution has a slightly alkaline reaction. Its sulphuric acid compound is crystalline.

The principal effect of duboisia is to cause dilatation of the pupils, in which property it has been found by some experimenters to equal, and to even excel atropia. It is said, as affirmed by Wecker, to be less irritant to the conjunctiva than atropia. The hypodermic injection of 0.001 gramme (gr. $\frac{1}{60}$) in watery solution prevents or diminishes the colliquative night sweats of phthisis.

Gubler, on the other hand, observed after the hypodermic injection of 0.0005 gramme (gr. $\frac{1}{120}$) of this substance, dryness of the throat and disturbances of sight, and after 0.001 gramme (gr. $\frac{1}{60}$) thirst, increased frequency of the pulse, redness of the skin and occasionally collapse. Sidney Ringer found that the subcutaneous injection of three drops of a solution of one part of extract of duboisia in four of water, given during the height of the action of pilocarpin, caused dryness of the skin in seven minutes, and in ten minutes a sufficient degree of dryness of the mouth to cause the patient to complain of it.

Untoward effects have also been already observed to follow the application of duboisia to the eye. Thus Davidson* reports eight cases in which the instillation of duboisia was followed by pathological symptoms of varying degrees of intensity, such as vertigo, restlessness and excitement, which developed even into violent delirium. In several cases dryness of the throat was also observed. Schöler† employed a watery solution of 0.05:5.0 without observing any symptoms of general intoxication. On the other hand he observed a well-defined follicular conjunctivitis in three or four cases after the application of the drug, and in two or three cases the instillation was followed by pain, redness of the conjunctivæ and immobility of the pupils.

*Davidson, Lancet. September 6, 1879.

†Schöler, Jahresbericht übres. Augen-Klink für 1878, Berlin, 1879.

ACONITINUM.

TUBERA—EXTRACT.—TR. ACONITI.

The effects of various preparations of aconitia prove that action of the same is modified by the method of preparing the alkaloid. While the German aconitia is not particularly poisonous, as compared with other poisonous substances, such properties are claimed by nearly every English experimenter for their domestic aconitia (Morson's Napellin or pure aconitine), which is probably prepared from the aconitum ferox, by a secret process.

While the maximum doses of the German aconitia, according to the German pharmacopœia, is 0.004 gramme (gr. $\frac{1}{15}$), Pereira* observed symptoms which are well nigh fatal, to follow 0.0015 gramme (gr. $\frac{1}{40}$) of the English aconitia. Notwithstanding the fact that the individuality of the person taking this active drug plays an important part in determining its action, the difference in the modes of action of the two varieties, as pointed out by Schroff, is too great to be left out of the question in determining the cause of the deleterious untoward action of the drug. Various degrees of such action have, however, been observed to follow each of the two varieties.

The English aconitia is said by Pereira to provoke heat and itching of the surface of the body, even when given in very minute doses. Turnbull† observed, after its external application, a pricking sensation on the part to which it was applied, and Schroff‡ found that a dilute alcoholic solution of this preparation applied to the forearm caused formication and pricking, without the evidence of any inflammatory change.

Cases of poisoning occurring as a result of the employment of the English instead of the German aconitin, are frequently recorded in literature. The English preparation should, in our opinion, be entirely discarded for internal use.

The German aconitia and other pharmaceutical preparations

*Pereira, Refer. bei Husemann, Pflanzenstoffe, 1871, p. 226.

†Turnbull, On the Preparations and Medical Employment of Aconitina. London, 1835.

‡Schroff, Journal für Pharmako dynamik, Toxikologie und Therapie, Bd. I., 1857, p. 365.

made out of the wolfsbane, cause, as Dworzak and Heinrich* experienced in their own persons, a biting, burning sensation of the tongue and lips, and salivation. An eruption of whitish vesicles has also been occasionally seen on these parts. There further not unfrequently occur a vague drawing sensation in the face, which may develop into a persistent pain, confined to the distribution of the trigeminus nerve, and be accompanied by a very annoying pricking sensation, occurring particularly on the chin and cheeks, but appearing also on the trunk and extremities. The mucous lining of the stomach and intestines is also irritated by this drug. Nausea, and even vomiting and borborygmi may occur. The frequency of the pulse is very markedly reduced. The continued use of the aconite gives rise to more remote effects, as headache, a greater or lesser degree of fullness of the head, buzzing in the ears, and general weakness—symptoms which disappear shortly after the suspension of the drug.

Although the exhibition of medicinal doses of the German and the other preparations of aconitia, does not generally cause an apprehension of symptoms threatening to life, pre-existing weakness of the heart's action, or other causes predisposing to the more intense action of the drug, may render the employment of direct therapeutic measures necessary. Contrary to the view formally entertained regarding its ill effects, L. Lewin† has shown that aconitia belongs to that class of cardiac poisons whose fatal action may be long postponed, and even entirely obviated, by prolonged artificial respiration. Artificial respiration must, therefore, be resorted to as soon as symptoms of dyspnœa and anomalies of the heart's action (irregularity, intermittency, etc.,) manifest themselves. In addition to this, and also in the slighter manifestations of the action of aconitia, the ordinary stimulants and diuretics may be employed to assist in the more rapid elimination of the drug. There is no direct antidote to aconitia known.

*Dworzak u. Heinrich, Prager Vierteljahrschrift, Bd. 42, p. 153 ff.

†L. Lewin, Experimentelle Untersuchungen über die Wirkung d. Aconitin auf das Herz, Berlin, 1875.

VERATRINUM.

RHIZOMA—TR. VERATRI.

That the alkaloid derived from the leaves of the white hellebore, as well as from the root of the plant, when given for therapeutic effect is not infrequently followed by a few pathological symptoms, is a fact which was familiar to the ancients and the physicians of the middle ages. These symptoms may supervene, in a greater or lesser degree of intensity, from any form in which the drug is administered.

A mere trace of the powder, which may be accidentally brought in contact with the nasal mucous membrane, causes violent and persistent sneezing, and may even give rise to profuse epistaxis. The conjunctiva is also violently affected when veratria, in the form of either an ointment or solution, is applied to it. The symptoms following the quite extensive external employment of this drug in neuralgia of the various nerve trunks, has furnished an opportunity for the careful study of its effects. An ointment of 0.6—1.0 gramme (gr. jx to gr. xv) of veratria to 30 grammes (℥ j) of lard, excites in a short time, not only at the seat of application but also in remote parts of the body, a sensation of pricking and increased heat. According to Reiche* this sensation gradually increases to burning, and through longer continuance of the application, a feeling of restlessness and anxiety supervenes. These symptoms may become permanent should the further employment of the veratria not be withheld, and the patient thus be deprived of sleep. Occasionally, also, a pruritic petechial or other vesicular eruption, which soon disappears with the discontinuance of the drug, has been observed on various parts of the body. The untoward effects may be more intense as a result of the internal exhibition of the drug. Veratria, owing to its property of lowering the frequency of the pulse and blood pressure, and reducing the temperature and the frequency of respiration, has been and is still employed in febrile affections, and particularly in pneumonia. In such cases it is given in doses of 0.003–0.0005 gramme (gr. $\frac{1}{20}$ to gr. $\frac{1}{120}$) and even more than the maximal dose of 0.01 gramme

*Reiche, Medic. Zeitung d. Vereins f. Heilkunde, 1839, 23.

(gr. $\frac{1}{6}$). But even small normal doses usually excite dryness of the mouth, burning in the throat, difficult deglutition, nausea, choking, and vomiting, and occasionally also salivation, colicky pains and diarrhœa, in which the discharges may be tinged with blood. Children, as stated by Forcke,* frequently vomit after the first dose, but adults rarely.

During the continued employment of medicinal doses a prickling or burning sensation occurs in remote parts of the body and particularly in the extremities. In many persons there occur vertigo and dimness of vision, and also a trembling and uncertainty of motion. In others completely developed collapse may ensue. Cerebral symptoms not unfrequently occur as a result of the employment of tr. veratr. virid. Thus Fleischmann† reports the case of a boy in whom dryness of the throat, great thirst and later temporary convulsive movements of the hands and fingers, raving and slight delirium, occurred after the exhibition of teaspoonful doses hourly of the following mixture: tr. veratri virid. gtt vj, mucilage 60.0 grammes ($\bar{3}$ ij).

Forcke observed a pustular eruption on the face, and particularly around the mouth, in several cases.

Eulenburg‡ noticed the formation of an abscess in one instance, after the hypodermic injection of an alcoholic solution of 0.0012–0.0015 gramme (gr. $\frac{1}{50}$ to gr. $\frac{1}{40}$), and usually after such an injection there occurred a slight and occasionally spotted redness and swelling around the point of entrance of the needle. The sensation of burning continued for several hours after the injection. Hiffelsheim also declares that pain and erythema occur as a result of the hypodermic administration of veratria. Sometimes the toxic symptoms develop into prostration.

The therapeutics of the untoward effects indicated, consist in the immediate discontinuance of the drug and the exhibition of analeptics, and particularly the liquor ammonii anisatus, in from 5 to 15 drop doses,§ or, according to Reiche (l. c.), black coffee with lemon juice. The drug must never, according to Troetscher,‖ be given during existing catarrh of the stomach.

*Forcke, Physiolo&isch—therapeutische Untersuchungen üb. d. Veratrin. Hannover, 1837.
†Fleischmann, Prager medic. Wochenschrift 1876, No. 10.
‡Eulenburg, Die hypodermatischen Injectionen, Berlin, 1875, p. 278.
§Husemann, Pflanzenstoffe, Berlin, 1871, p. 510.
‖Troetscher, Wiener Medicin. Halle, 1863, p. 487.

EXTRACTUM FABÆ CALABARICÆ

ESERIN S. PHYSOSTIGMIN.

The untoward effects which manifest themselves in connection with the external application of the calabar bean to the eye, have been clearly demonstrated by the classic experiments of A. v. Græfe.* According to him this drug penetrates the cornea and being dissolved in the fluids of the eye, exerts its influence directly on the iris and ciliary muscle. He found that immediately after the instillation of a solution of the alcoholic extract in glycerine, there ensued a biting sensation in the conjunctival sac and a corresponding reflex action on the orbicularis muscle, and the lachrymal secretion, the intensity of these effects varying with the individuality of the person and the strength of the solution. Following this, when the contraction of the pupil and the accommodative changes set in, a painful sensation of contraction, partially along the equator of the globe and partially in front of it in the region of the ciliary body, is complained of. Others refer to a nervous contractile pain in the entire eye ball, which spreads, after the manner of the ciliary neurosis, along the course of the supraorbital nerve, assuming the nature of migraine on the corresponding side of the head. Græfe leaves it undecided whether this pain is most dependent on spasm of the tensor or sphincter.

He made no observation touching more remote effects. Should such have occurred they would, most naturally, have been ascribed to the passage of the drug along the tear ducts.

Following the internal exhibition of small doses of the extract of calabar bean, as they are employed in neuralgia, tetanus, epilepsy, and also in atropia and strychnia poisoning, Fraser† observed an intense pain in the epigastrium, as well as vertigo, and weakness of the muscles of the extremities, and weakening and irregularity of the heart's action. The latter symptom may take on the nature of paralysis, but is, however, of but short duration.

Leven‡ noticed nausea and general uneasiness as a result of small doses of physostigmin.

*A. v. Græfe, Archiv f. Ophthalmologie, Bd. ix., 1863, III., p. 87.

†Fraser, Transactions of the Royal soc. of Edinburgh, XXIV., 1867, 73.

‡Leven, Journ. de Pharmac. et Chimie, I, 70.

AMYGDALÆ AMARÆ.

AQUA AMYGDAL. AMARARUM.—AQ. LAUROCERASI.

Bitter almonds are said by Stillé* occasionally when given in medicinal doses to cause a copious urticarious eruption. Gregory also observed a similar eruption on himself after eating a bitter almond. This effect is traceable to the presence of hydrocyanic acid in the almond. This is corroborated by the fact that water containing hydrocyanic acid, such as bitter almond water and cherry laurel water, also give rise to similar untoward effects.

Small doses (10 drops) of cherry laurel water may give rise to irritation of the throat and an increased flow of saliva. Should this quantity be somewhat exceeded, as so often happens in practice, or should small doses be frequently repeated, there occur, according to Coullon,† nausea, vomiting, vertigo and headache. In connection with the sensation of dizziness, there may also occur buzzing of the ears, labored breathing, and great depression.

In view of this fact, and of the additional fact of the dissimilar strength of waters containing hydrocyanic acid as well as of the varying degree of individual susceptibility to the action of the same, Köhler,‡ very properly cautions against the usually reckless administration of this drug as an antispasmodic. Trousseau and Pidoux most correctly indicate its value when they say that it is often dangerous, nearly always useless, and exceedingly rarely curative.

SEMEN COLCHICI.

TINCTURA—VINUM COLCHICI.

The efficacy of the preparations of colchicum is dependent on the percentage of colchicin which they contain. This, however, varies with the season of the year during which the drug is gathered.

*Stillé, Therapeutics and Materia Medica. Philadelphia, 1874, I., p. 175.

†Coullon, Recherches et considérations médic. sur l'acide hydrocyanique. . . . . Paris, 1819.

‡Köhler, Handbuch der physiolog. Therapeutik, Göttingen, 1876, p. 1 33.

According to Aschoff and Bley* the colchicum root contains the largest percentage of colchicin in July and August. It is not impossible that this circumstance is responsible for the abnormal symptoms which appear after the therapeutic employment of colchicum gathered in the autumn.

Small doses (0.1–0.3 gramme [gr. jss to gr. jvss]) of the seeds have been often observed to cause burning in the throat and stomach, ptyalism, distressing nausea, and serous diarrhœa with tenesmus. Some or all of these symptoms sometimes appear only after the prolonged use of the drug, but occasionally also occur soon after its exhibition. There are not infrequently, though with greater inconstancy, associated with the symptoms named, fullness of the head, headache and vertigo. The secretion of urine may also be attended with pain.

The symptoms referable to the gastro-intestinal canal are due to the local irritation of the drug. In support of this view are the established toxic effects of large doses of the drug on man and beast, viz., intense inflammatory changes in the mucous membrane of these organs.

The untoward effects described most frequently occur after the use of the wine of colchicum seeds, the prescribed dose of which (2 grammes [3 ss] per dose, or 6 grammes [3 jss] per diem) is certainly excessive, should the wine have been prepared from the fresh, active plant.

The action of officinal colchicin, of the Phar. Austrica, which is readily soluble in water, has been observed on man, by Schroff.† After the exhibition of 0.01 gramme (gr. $\frac{1}{6}$) of this principle, there was at first a bitter and afterwards irritating taste, which was soon followed by eructation, nausea, retching and salivation. After 0.02 gramme (gr. $\frac{1}{3}$) there occurred in addition to these symptoms, vomiting and diarrhœa with tenesmus, and later chills and sleeplessness.

In the subcutaneous application of colchicin as recommeded by Badia, and later by Heyfelder,‡ in rheumatic affections, the drug produced an intense burning and itching on the seat of the injection, which usually lasted only half an hour, but often longer. In one-

*Aschoff und Bley, Archiv d. Pharmacie, Januar, 1857.
†Schroff, Oesterreichische Zeitschr. f. pr. Heilkunde 1856, II., 22.
‡Heyfelder, Berl. Klin. Wochenschrift No. 15, 2877.

third of all cases there occurred a local inflammation of the skin, with slight swelling and tenderness on pressure. In view of this peculiarity of the colchicin, it is advisable not to employ it during high febrile disturbance, or to apply it to inflamed parts; in the latter condition, if employed at all, it should be applied only at some distance from the seat of the inflammation. In a very sensitive person, slight dysuria was several times observed after this medication.

FOLIA DIGITALIS.

EXTRACTUM—TINCTURA—UNGUENTUM DIGITALIS.

Digitalis shares with only a few other drugs the property, which is perhaps due to its abnormally slow elimination by the kidneys, of continuing its action in the body during a relatively long period, and, therefore, of giving rise, through the continued administration of repeated doses, to cumulative action. The latter may under certain circumstances give rise to threatening appearances and even to symptoms of positive poisoning. Among the latter are the following: headache, dryness in the throat, nausea, choking, and, in well marked cases, buzzing in the ears, disturbances of vision, manifesting themselves in muscæ volitantes, amblyopia or diplopia, and later in dizziness, fainting, vomiting, diarrhœa, sleeplessness, a thread-like, scarcely perceptible, irregular pulse, and a quite distinct fall in the temperature of the body, due to lowering of the activity of the circulation. A headache was particularly observed to occur after 0.03–0.09 gramme (gr. ss to gr. jss) of the drug. In some persons 0.15 gramme (gtt. iij) of the tincture of digitalis is sufficient to arouse the symptoms mentioned.

In the absence of any known direct antidote to digitalis, treatment of these effects must be symptomatic, as the exhibition of stimulants, counter-irritants, etc. In view of the property indicated, through which death may suddenly occur as a consequence of cardiac paralysis, prophylactic measures must receive especial attention, especially when the drug is to be administered for some time, and its use must be suspended on the first appearance of abnormal subjective symptoms.

In the opinion of Durosiez, some of the unexpectedly fatal cases

of inflammation, occurring during a course of treatment with strong infusion of digitalis, are traceable to the poisonous action of the drug.

An observation of Traube's* regarding the occurrence of a skin affection after the employment of digitalis, should be mentioned as something which seldom happens. In a case of pericarditis and pleuritis the patient was given between the fourth and the sixth days of his sickness 3.75 grammes (gr. lvj) of digitalis in infusion. In four days after the last dose there appeared, the body being of normal temperature, an erysipelatous affection of the face which, five days later, resulted in an excessive flake-like desquamation. In a second case, of pleuropneumonia, 4.08 grammes (gr. lxj) of digitalis were given in an infusion in five days. Four days after the last dose of digitalis the patient, who up to that time had been free from fever, experienced an exacerbation of fever, and on the fifth day there appeared on the trunk, the supinator surfaces of the forearm and back of the hands, a papular eruption, consisting of quite prominent, carmine-red spherical spots, the color of which disappeared on pressure, the majority of them uniting in confluent patches over the surface of the skin. On the following day desquamation in quite large flakes occurred on the face, while new eruptions were observed on the arms and neck. In still four days the eruption had almost entirely disappeared, and it was only in the course of a typhoid affection which subsequently developed, that desquamation of the trunk and extremities took place in large flakes.

Schuchardt† observed a similar eruption in a robust young man, spreading over his entire body, after he had taken digitalis for some time for the relief of endocarditis. This same person, having resumed the medicine a year later, was attacked with the same eruption and of equal intensity.

It is, perhaps, not unimportant, for a proper understanding of the manner of the occurrence of this affection, to instance the fact that the officinal digitalis ointment (ext. digitalis 1 part, unguent. ceræ 9 parts), but in a greater degree a salve prepared with lard and fresh digitalis leaves, may, when several times rubbed into the skin, excite a slight inflammation and papular eruption. Its appli-

*Traube, Charité-Annalen, Jahrg. I., p. 622 u. Jahrg. II., p. 19. Beiträge zur Pathologie, d. II., 1. Abth., p. 130, 156, 164.

†Schuchardt, Hændbuch der Anzneimittellehre, Braunschweig, 1858, p. 553.

cation to skin deprived of its epidermis excites, as a matter of course, a more violent inflammation. It is, therefore, conceivable that in connection with a certain individual disposition the accumulation of a large quantity of the active principle of the digitalis in the circulation, may excite the same irritative effect on the skin as the external application of the drug. This explanation accounts for the circumstance, noted in cases reported by Traube, that the exanthem first appeared after the use of the digitalis had been suspended.

The following statement of Reil* is worthy of note: cumulative effects are very seldom noticed after the employment of digitalin, because there appear as harbingers of intolerance of the drug, a sensation of weakness in the epigastrium, an inclination to vomit, exhaustion, dimness of vision and heaviness of the head, which admonish to a discontinuance of the drug.

CHLORALUM HYDRATUM—CRYSTALLISATUM.

The occurrence of untoward effects after the internal exhibition of chloral hydrate, is, in view of the very extensive employment of this drug, not very frequent. This is the more to be wondered at because of the fact noted by Richardson† that its habitual use as particularly noted in England and America, even in "chloral drinkers," causes no habituation to the effects of the drug, and gives rise to no deleterious consequences so long as the standard doses are not exceeded. Other observers have confirmed these observations on the basis of reports from insane asylums, from which he also established the fact that the employment of a pure preparation for its hypnotic action for even a prolonged period, neither necessitates any increase of dose, nor produces any unpleasant effects as is the case with opium and its alkaloids. The use of impure preparations of chloral, however, in consequence of the formation of deleterious, chlorinated substances and increasingly acid reaction, gives rise to perverse therapeutic effects.

The bad quality which is usually peculiar to those preparations which are not well crystallized, is probably one of the causes of fatal effects which are reported in literature as following one or more

*Reil, Materia Medica der reinen Pflanzenstoffe, Berlin, 1857, p. 155.
†Richardson, Medical Times and Gazette, February, 1871.

medicinal doses. It is a notable fact, in this connection, that during the first years of the employment of chloral, many of such cases were reported, while on the other hand with the more perfect means of manufacture of recent times, such accidents are very rarely described. Should such cases so occur they are in the first place ascribed to the impurities of the preparation, inasmuch as we are familiar with several organic combinations with chlorine which, even when given in small doses, are capable of deleterious effects. At the same time individual predisposition to the occurrence of such symptoms also plays an important rôle, and the condition of the absorptive organs is particularly to be taken into consideration.

It is a noteworthy characteristic of the fatal cases reported by various authors as resulting from chloral hydrate, that these almost always follow the exhibition of the drug immediately or at a very short interval, and usually in cases in which there is much anxiety. Nötel,* among others, reports such accidents after the exhibition of 4 grammes (℥ j) of chloral, Jolly,† in two insane persons after 5 grammes (gr. lxxv) each, Marsh,‡ in four persons, the majority of whom were drunkards, after 3 grammes (gr. xlv), and Fürstner § in a girl after but two grammes (gr. xxx). The autopsies, as published, furnished no insight into the causes of death.

In rare cases, according to Kirn,‖ there occur disturbances of respiration, which may increase from a sense of fear, anxiety and shortness of breath, to attacks of dyspnœa and even asphyxia. So also Shaw** observed spasmodic breathing and irregular action of the heart after about one gramme (gr. xv) of chloral. The mucous lining of the air-passages, according to Marsh, suffers change after an ordinary dose of chloral, as evidenced by the bronchitis which he observed.

Much more frequent than the symptoms mentioned is the irritation of the conjunctiva which follows one or more doses of chloral. Redness and swelling of the conjunctiva are noticed, which, however, disappear shortly after the discontinuance of the

*Nötel, Virchow-Hirsch's Jahresbericht f. d. ges. Medicin, 1872, II., p. 11.
†Jolly, Bair. ärztl. Intelligenzblatt, 1872, No. 13, 14.
‡Marsh, Virchow-Hirsch's Jahresb., 1875, I., p. 479.
§Fürstner, Archiv. f. Psychiatrie, Bd. VI., 1876, p. 344.
‖Kirn, Allgem. Zeitschr. f. Psychiatrie, 1872, p. 316.
**Shaw, Virchow-Hirsch's Jahresber., 1871, I., p. 334.

drug. Steinheim* reports the case of a lady whom he treated for asthmatic attacks, who experienced a severe disturbance of vision on each of three occasions after the employment of chloral. It manifested itself as dimness of vision or complete blindness.

The "chloral rash" described by Schüle† which manifests itself in flashes of heat, and congestion of the head with injection of the conjunctivæ, occurs only when the chloral is followed by a draught of an alcoholic beverage.

Curschmann‡ reports, among other untoward effects, swelling of the epiglottis and false vocal cords, and Reimer§ the occurrence of bed sores. The ætiological connection of the latter symptom with the use of chloral is, however, as yet, doubtful. According to Reimer, the bed sore resulting from chloral differs from the ordinary variety due to long continued pressure, in the fact that it occurs after very light external pressure, and that it may occur, develop and spread deep into the subcutaneous tissue, the epidermis and cutis remaining intact.

Quite peculiar cases are reported in the literature of chloral, in which icterus is said to have resulted from the use of the drug. Thus Wernich‖ reports four observations in which an existing jaundice became intensified after the use of chloral, and also the case of a tippler in whom four grammes (ʒ j) of chloral hydrate excited a fresh attack of icterus. Arndt** also observed the appearance of jaundice in a paralytic after he had employed the drug for fourteen days, it passing off with the suspension of the drug and recurring with its renewal. The opinion of Gellhorn†† that an atrophied condition of the liver of a quite peculiar nature, may, among other affections, occur as an expression of the idiosyncratic action of chloral, is somewhat hypothetical. This observation is the only one of the kind recorded. In addition to the symptoms which have been recorded, there have been observed in some persons either polymorphous or simple eruptions, following either immediately after the exhibition of variable doses of chloral, or

*Steinheim, Berliner, Klin. Wochenschr. 1875, p. 77.
†Schüle, Zeitschrift f. Psychiatrie, Bd. 28, p. 4.
‡Curschmann, Deutsches Archiv f. Kl. Medicin. Bd. VIII, p. 151.
§Reimer, Zeitschr. f. Psychiatrie. Bd. 28. p. 316.
‖Wernich, Deutsches Archiv. f. Klin. Medic, Bd. XII., p. 32.
**Arndt, Archiv. f. Psychiatrie, Bd. III, Heft 3.
††Gellhorn. Zeitschrift f. Psychiatrie, Bd. 28, p. 625.

occurring some time after. These may be classified as the erythematous, urticarious and the eczematous varieties.

1. *The erythematous form* is relatively the most common. There is usually observed on the face and neck an eruption of the nature of a diffuse hyperæmia. On the other parts of the body, the trunk and extremities, the erythema generally occurs in the form of irregularly outlined, roseola-like or dark red spots, bearing a striking resemblance to purpura. According to Schüle (l. c.) it appears to follow, by preference, the course of the nerve trunks. It disappears with the suspension of the drug. Brown* observed in one case an inflammatory redness which spread uniformly over the whole body, while Husband,† in the case of a female patient who took two doses of 1.3 gramme (gr. xx) each, daily for eight days, and two doses of 2 grammes (gr. xxx) each, for five days, observed a scarlatiniform eruption, occurring with high fever and hyperæsthesia of the skin, and being followed after its subsidence by abundant desquamation. Köbner also reports a case in which there occurred, after the prolonged employment of chloral, not a simple hyperæmic redness, but an erythema exsudativum which spread over nearly the whole surface of the body. It was quite scarlatiniform in its appearance, differing only in the fact that the skin was more swollen and infiltrated. The eruption burned and itched, and disappeared with desquamation, the use of chloral being continued, only after four or five weeks.

2. *The urticarious form* has been observed by Gauchet‡ and Chapman § among others. The latter observed its occurrence in a lady who had taken a gramme (gr. xv) of chloral each evening for fourteen days. After this time there occurred an erythema which disappeared with the suspension of the drug, and when it was again given, two days later, rapidly covered the skin of the entire body with wheals, which were the seat of a sensation of heat; simultaneously with this was hyper-secretion of the conjunctivæ. Those eruptions, which have been classed as papular and which occur under the same conditions, must be classed with this urticaria-like form. Thus Arndt (l. c.) observed a papular eruption which occur-

*Brown, Lancet, 1871, Vol. I., p. 440.
†Husband, Eod. loco., 1871, No. 25.
‡Gauchet, Bulletin génér. de Thérapeut. 1871, p. 429.
§Chapman, Lancet, 1871.

red after chloral had been used for eight days, appearing first on the extensor surfaces of the upper extremities, but spreading, later, over the whole body. This appeared and disappeared with the use and disuse of the drug. Kirn (l. c.) observed a similar eruption which was confined to the arms.

3. Under the continued use of chloral the nodules may develop into vesicles with serous or purulent contents, and these, when they burst, present a complete resemblance to *eczema*. This, however, happens very rarely, and the only case recorded seems to be that observed by Kirn, and even this is not a pure case, inasmuch as during the existence of the exanthem, quinia, a drug which is itself capable of giving rise to a variety of dermatoses, was given hypodermically. In a robust person, suffering from puerperal mania, there appeared on the ninth day of the exhibition of chloral, with febrile disturbance, an exanthem, with simultaneous swelling of the face, cheeks, eyelids and ears. It disappeared after a time, and reappeared on the renewal of the chloral, when the skin presented, in a very variable manner, sometimes an impetiginous, sometimes a weeping, and again a squamous form of eczema and ichthyosis, in which the desquamation was not confined to a short period, as is the case with the acute exanthemata, but continued for many weeks, large flakes of epidermis being shed from all parts of the body. At a later stage of the affection the disturbances of the skin manifested themselves in a distinct falling of the hair, and a gradual shedding of the nails of the upper and lower extremities.

Schüle and others have ascribed as the direct cause of the skin disease a paralysis of the vaso-motor nerves by the chloral. Efforts have not been wanting, as in the case of other drugs, to explain the occurrence of these untoward effects of chloral. Those authors who have undertaken such explanation, regard the untoward effects as due to a chronic poisoning of the blood, and maintain that they cannot be developed until the body has become saturated with the drug. According to this view chloral must possess a cumulative action similar to that which obtains in the case of digitalis. This view will, however, on closer consideration of the existing conditions, be found to be untenable. By a blood poisoning we understand a chemical or physical change of such a nature in the constituents of the blood that they are no longer in a condition which fits them for a proper discharge of their normal functions. In this sense of the term one

may regard as blood poisoning that condition induced by the inhalation of carbonic oxide or sulphuretted hydrogen, by the ingestion of too large doses of chlorate of potassium, or the introduction of other heterogeneous substances into the circulation. But in all these cases there occur changes in the blood whose existence may be demonstrated either by the spectroscope or the microscope, or even by simple unaided inspection. In the case of chloral, however, none of these methods have as yet been able to detect any evidences of such action, and we are, therefore, not justifiable in admitting the claim of blood poisoning. There can also be no definite standard fixed for such saturation of the system with chloral as shall give rise to the untoward effects indicated, inasmuch as these occur in some instances even after but a single small dose. On the other hand, if such a degree of saturation should be reached, the cumulative action of chloral would occur at the same time, and this would suffice to ensure the sedative and hypnotic effects of the drug without the necessity of its further administration. That this is not the case needs scarcely to be mentioned. There must, therefore, be other conditions for the occurrence of the symptoms named. They are most effectually explained by the general facts as detailed in the introduction to this work. It is probable that the chloral, or the products of its decomposition, which find their way into various organs, exert on some persons, perhaps either because of abnormal vascular supply or other individual property, a direct irritating or paralytic effect. This continues as long as the products remain in the system. Bodily conditions which either prevent or cause a retardation of elimination of the products of waste, may also favor its occurrence.

No particular therapy is necessary for the relief of the effects of chloral as described, inasmuch as they disappear spontaneously with the suspension of the drug. In the case also of the fever which usually attends the chloral eruption, there is no therapeutic interference demanded, as, according to Schüle, neither quinine nor cold baths are followed by material benefit. It should also be mentioned in this connection, that quinine is apt to induce a variety of complications in those in whom there is a predisposition to the occurrence of drug eruptions, and that it is, therefore, better to entirely abstain from its employment.

CHLOROFORMUM.

Soon after the introduction of chloroform into medical practice, and in the midst of its progress through the civilized world, cases became known in which the narcotized persons never awoke. If in the beginning of the employment of this drug fatal cases were not reported, because of a suspicion on the part of the physician in attendance that he was himself personally responsible for the misfortune, the increasing number of such accidents soon made it probable that there must be certain conditions which are to be regarded as causes of the so-called "chloroform deaths." These conditions are even yet, in spite of the large number of the most careful clinical and experimental observations, not determined with any degree of certainty. On the other hand the symptomatic appearances which precede or accompany death from chloroform have been closely observed and described.

In a small proportion of the fatal cases of chloroform narcosis, death occurs without any warning prodromal symptoms. In such cases the pulse ceases suddenly, during complete or incomplete narcosis, respiration ceases in one or two minutes, the face becomes pallid, the pupils dilate and death ensues. Generally, however, the warning is given of a disastrous result of a narcosis by one or more premonitory symptoms. There occur persistent vomiting, decided pallor of the face, labored and occasionally stertorous, ringing respiration, extreme mydriasis, failure to excite reflex action through irritation of the conjunctiva of the globe, spasmodic muscular movements, a certain muscular rigidity, and a small, scarcely perceptible pulse, which, in spite of the contractions of the heart, entirely disappears. Respiration ceases either simultaneously with or before the stoppage of the pulse, or it may continue after the pulse ceases. In the former case death must be attributed to asphyxia, in the latter to syncope. Billroth* observed in a case of death from chloroform during convulsions, that the hæmorrhage from a wounded finger ceased just before the event.

Kappeler† has collected with great care the statistics of death occurring from chloroform in so far as these have been published. He reports 101 fatal cases, of which 78 were in males and 23 in

*Billroth, Wiener Medic. Wochenschr. 1866, No. 46.

†Kappeler, Anæsthetika. Deutsche Chirurgie von Billroth und Lücke, Lief. 20, p. 100 uff.

females. The most fatal was between the ages of 46 and 60, 24.7 per cent. of the deaths occurring in patients between those years. The next most fatal age was from 31 to 45, between which years the deaths were 20.7 per cent., while in only one fatal case was the patient over sixty and in one also under two years of age. Death occurred before complete anæsthetization in 43 cases, and during complete narcosis in 47. In 11 cases there is no statement on this point. In 56 fatal cases of anæsthesia the chloroform was inhaled from a cloth or lint, in five cases from Esmarch's "chloroform basket," and in an equal number of cases from Clover's inhalation apparatus. The quantity of chloroform employed varied in 46 cases between 20 drops and 30 to 60 grammes (℥ j to ℥ ij), the average quantity being 11.1 gramme (℥ ij ¾). Of 20 cases, regarding which the facts are given, death occurred in 10 within from six to fifteen minutes, and in five after from one to three minutes.

The anatomo-pathological changes hitherto detected afford, because of their inconstant and general nature, no clear insight to the immediate cause of death. The experiments of the English Chloroform Committee, which were conducted chiefly on dogs, revealed many similar facts to those observed in the autopsies of patients dying from chloroform, viz.: a great fullness of the cavities of the heart with blood, those of the right side being more distended than those of the left. In several cases there were found, as Langenbeck among others as early as 1848 declared there might be, gas bubbles in the veins of those dying from the effects of chloroform. This fact led some French investigators to attribute death from chloroform to the development of chloroform vapors in the veins, or to embolism in the pulmonary capillaries from this cause. More recently renewed observations on the accumulation of gas has led to experimental investigation of this phenomenon. V. Recklinghausen, in three fatal cases of chloroform poisoning, in which breathing continued for some time after cessation of the pulse, found gas bubbles in the larger venous trunks and the heart, in spite of the fact that there was no discoverable trace of decay or decomposition in the body. Sonnenburg* was able, in the experiments which he undertook on animals on the strength of this observation, to develop a gas, which he showed to be nitrogen, in the vessels, but was unable

*Sonnenburg, Tageblatt der Naturforscherversammlung zu Baden-Baden, 1879, p. 29.

to determine the precise conditions and properties necessary to the occurrence of this formation. One may, in his opinion, regard it either as the mechanical separation of the nitrogen, or as the liberation of the same, through peculiar pressure, in the vessels and in the presence of chloroform.

This demonstration of the liberation of a gas in the vessels after the inhalation of chloroform, is, when considered from a general toxicological point of view, highly important. It, however, brings us no nearer a knowledge of how it is that in rare cases death occurs from chloroform narcosis, in spite of the greatest care and watchfulness, while on the other hand other patients may be anæsthetized with the same chloroform and perhaps very carelessly, without the occurrence of any ill effects. As might have been naturally expected there have been, in the course of time, a great variety of circumstances alleged as causes of the bad or fatal results of chloroform narcosis. We have, however, not as yet been in a position to regard any one or more of them as the general or sole etiological factor. It is thus impossible to concede the truth of such a positive statement as the following, first made by Sédillot* and later by Yvonneau†: "le chloroforme pur et bien employé ne tue jamais," inasmuch as there are probably other factors which, under certain circumstances, may determine the ill results of the anæsthesia.

The many conditions which have hitherto been held responsible for death from chloroform, may be arranged under three heads, as follows:

1. The quality of the chloroform.
2. The manner of its administration.
3. The mental and physical condition of the patient.

1. *The bad quality of the chloroform* is usually regarded as the chief factor in the causation of ill effects or death from its employment. It is a familiar fact that chloroform may, either through design or accident, be adulterated in many ways. The former consists in the addition of alcohol or ether, and the latter may be the result of the method employed in the manufacture of the drug or of the spontaneous decomposition of the chloroform by the action of light. The impurities which occur in the manufacture of chloroform consist chiefly either of a mixture of acetyl and its chlorine

*Sédillot, Gazette de Strassbourg, 1851, 7., 11.
†Yvonneau, De l'emploi du Chloroforme, Paris, 1853.

derivatives or fusel oil. These may be detected by the occurrence of a black or red color on the addition to chloroform containing them, of concentrated sulphuric acid. The products of the spontaneous decomposition of chloroform may be: free chlorine (detected by the appearance of a red color when such chloroform is dropped into a dilute solution of the iodide of potassium), hydrochloric acid (the chloroform containing it becoming cloudy on the addition of nitrate of silver), and hypochlorous acid (the presence of which is detected by the bleaching of blue litmus paper when dipped in chloroform). In addition to these there may also be found higher chlorine compounds, as for instance, ethene chloride (Dutch liquid), ethyl chloride, tetrachloride of ethene, ethidene chloride, trichlorethane, tetrachlorethane, chlorallyl, amyl chloride, and aldehyde and amylene.

All these impurities of an organic nature, the majority of which may be demonstrated by qualitative analysis, usually betray their presence by the change in the specific gravity and the boiling point of chloroform. Officinal chloroform has a sp. gr. of 1.496; absolutely pure chloroform at 15°C. (59°F.) a sp. gr. of 1.502; at 17.5°C. (64°F.) a sp. gr. of 1.497; and at 20°C. (68°F.) a sp. gr. of 1.493. The presence of 0.5 per cent. of alcohol reduces the sp. gr. to 1.493 at 15°C. (59°F.) and 1 per cent. to 1.485. In the same manner ether, ethene chloride and amylene reduce the specific gravity, while tetrachlorethene, tetrachlorethane and trichlorethane raise it. The boiling point of officinal chloroform is between 61° and 62°C. (143°F.). It is lowered by ethylic chloride, ether and amylene, and raised by alcohol, ethylenic chloride and the rest of the higher chlorine compounds mentioned above. Chloroform prepared from chloral and also the English chloroform, both of which are said to undergo no decomposition, have a specific gravity of less than 1.49.

Nearly all of the higher compounds with chlorine which have been mentioned, cause untoward effects when inhaled, and are quite capable of causing accidents when administered in the presence of certain predisposing bodily conditions. While it is true that these by-products have, heretofore, been discovered in but a few of the cases which have been recorded, it appears that as a rule no very accurate investigation of them has been made. The observation

of Bartscher* on the difference between the action on man of pure chloroform and that containing foreign chlorinated products, is worthy of notice. While he was able to very readily procure narcosis with fresh chloroform, a sample which had stood for several weeks caused a series of evil effects both during the narcosis and in the course of the next twenty-four hours. The changes which the chloroform suffered in standing were first manifest in the loss of the somewhat pleasant sweetish taste and by its causing a burning sensation in the nose and throat which gradually developed into a feeling of unpleasant irritation. In such cases the presence of hydrochloric acid, alcohol and ethene chloride could always be demonstrated. The deleterious untoward effects disappeared with the use of rectified chloroform. Berghmann† found in a sample of chloroform from the employment of which death occurred before full anæsthesia was secured, small quantities of chloride of allyl. In another case reported by Hüter,‡ in which death occurred during complete anæsthesia, only a third of the chloroform administered was distilled over at the proper temperature (62° Cels. [143⅗°F.]). The remainder boiled only at 70° and 75° Cels. (158° and 167°F.), and even at 80° Cels. (176°F.), there was a not inconsiderable residue. Neither hydrochloric acid nor free chlorine was among its contents. It seemed to have been prepared from impure alcohol, and contained chlorinated products. From the occurrence of effects of this nature one cannot but regard the bad quality of chloroform as an important factor in the causation of death, especially when the patient was robust and suffering from no pre-existing disease. In order to ensure certain security against effects such as reported, the custom of Hüter to administer only such chloroform whose boiling point has been determined, is to be recommended.

2. *The improper manner of its administration*, that is, the inhalation of chloroform without a proper admixture of atmospheric air, is much more certain than impure chloroform to cause threatening symptoms or death. In England, particularly, the greatest importance is attached to this factor in the causation of death from chloroform. Thus the English Chloroform Committee§ gave expression to the opinion that those cases in which death occurs

*Bartscher, Berl. Klin. Wochenschr., 1866, p. 325.
†Berghmann, Ref. by Kappeler, l. c., p. 88.
‡Hüter, Berl. Klin. Wochenschr., 1866, No. 30.
§Medico-Chirurg. Transact. xlvii., 1864, p. 323.

before the stage of anæsthesia as well as those in which death occurs from syncope before the beginning of the stage of excitement, are due to the sudden inhalation of too concentrated vapors of chloroform. Holmgreen* has more recently succeeded in showing, by experiment, that the retardation or suspension of the heart beat from the inhalation of a too concentrated condition of the chloroform vapors at the beginning of narcotization, results from a reflex influence from the branches of the trigeminus distributed to the nasal and pharyngeal mucous membrane on the vagus. Should these parts be protected from contact with the chloroform vapors, as may be done by administering them through a tracheal canula, these disturbances of respiration and the pulse, as the Chloroform Committee found, do not appear. Lallemand, also, and Perrin† and Duroy, observed the speedy occurrence of death in animals which inhaled the too concentrated chloroform vapors. A mixture of 4 parts of chloroform with 100 parts of atmospheric air was found by them to be innocuous, while one of 8:100 was deadly in its effects. In order to obviate the danger of too concentrated chloroform vapors, the Chloroform Committee laid down the following mixture as the standard of strength for inhalation: chloroform 3½ parts to 100 parts of atmospheric air, and as the maximum a mixture of chloroform 4½ parts with 100 of air.

For the preparation of this or similar mixtures Clover and others have devised various apparatuses. These are, however, too complicated and furnish a no more certain protection against the dangers of chloroform, which lie in the concentration, than the ordinary chloroform basket in the hands of a competent person. The dangers which are due to concentration may with certainty be avoided by giving the chloroform gradually, beginning with small quantities and allowing a free admission of fresh atmospheric air to the air passages.

P. Bert‡ traces nearly all of the dangers which attend anæsthetization by chloroform, to the methods of its administration which have heretofore been in vogue. He calls the interval between the anæsthetizing and the fatal dose, the "turning zone"

*Holmgreen, Virchow-Hirsch's Jahresbericht 1867, I., p. 450.

†Lallemand, Perrin, Duroy, Du rôle de l'al cool et des anesthésiques dans l'organisme Paris, 1860.

‡P. Bert, Communication sur les Anesthésiques, Bullet. de l'Académ. de Médec. Nov. 1881.

(wendezone, zone maniable), that is the time when it still lays in the power of the surgeon either to restore the patient to a consciousness of pain or to permit him to die. As regards the limits of this zone, he found that the fatal dose is always double that required to produce anæsthesia. According to this the inhalation of the anæsthetic is most dangerous the limits of whose "Zone maniable" is most contracted. In the pernicious method of anæsthetization heretofore employed the patient inhales alternately a mixture of the anæsthetic and atmospheric air which depends for its proportions on the absorptive power of the basket or compress, and the distance between the apparatus and the respiratory organs. This mixture is sometimes in less than anæsthetic proportions and sometimes in the "wendezone," and may also approach the fatal dose or even reach it. Should the inhaling apparatus be removed on the appearance of threatening symptoms, the composition of the mixture in the lungs is forthwith changed at the next inspiration, but it is not always possible to avert the fatal issue.

According to P. Bert the activity of the chloroform inhaled does not depend on the actual amount taken, but rather in the proportion in which it exists in the atmosphere inspired. He, therefore, regards the methods of inducing anæsthesia heretofore employed as incorrect, and proposes to have the anæsthetic inhaled through a small mask and a tube from a zinc box holding from 200 to 300 liters (50 to 80 gallons) and in which definite proportions of atmospheric air have been mixed with the anæsthetic in the form of vapor or gas. In this manner every danger may be obviated, and even the watching of the pulse and respiration rendered unnecessary.

It is very manifest from this that P. Bert leaves entirely out of consideration the powerful influence of individuality which may certainly be sufficient to induce unfavorable action in some persons.

3. *The mental and physical condition of the patient* is a much more important factor in the causation of dangerous symptoms during anæsthetization by chloroform than both of the factors already mentioned. But we are not any more justified in regarding the bad quality of the chloroform or its improper administration, as the only cause of all the deaths from chloroform, or of its untoward effects, even, than we are in holding that any of the conditions about to be mentioned is the exclusive factor in the causation of the perverse action of the drug. The several authors have held the following

conditions, pertaining to the mental and physical spheres, responsible for such action :

a. The idiosyncrasy against chloroform.

Clemens,* Billroth,† and Dénonvilliers.‡ The latter, particularly, declares that the death from chloroform which occurs with lightning rapidity after a few inhalations of the drug, is due to idiosyncrasy. He cites as analogous occurrences the specific action of other drugs, as iodide of potassium, etc., upon certain persons. Clemens claims to have frequently met this chloroform idiosyncrasy. It manifests itself in persons who submit to the use of chloroform through an earnest desire for a painless operation, but who, after the first inhalation spring up declaring that they had rather undergo the operation without the anæsthetic. Dénonvilliers is of the opinion that the peculiar susceptibility to the toxic effects of chloroform which exists in some persons is but temporary, inasmuch as patients who some time before have borne the drug very kindly during a first operation have succumbed at its second administration. An attempt was already made in the introduction to this work to furnish a foundation for a conception of the term "idiosyncrasy"—a term in itself without significance. If we conceive it to refer to a certain physical condition, which is either congenital and consisting of a falling short of the normal standard of the structure or an improper arrangement of the different parts of the body, or is but temporary and a consequence of functional disturbances in individual organs, we are able to explain the deviation from the normal action of chloroform, as, for example, the ready occurrence of reflex stoppage of the heart beat, the occurrence of eruptions or of vomiting in given cases.

b. Psychical depression.

According to the views of the English Chloroform Committee, such persons as are under the influence of any emotion, whether it be fear, fright or care, etc., are peculiarly liable to succumb to the action of chloroform. The same is true of persons who have suffered injury from the action of any sudden external force, or, in other words, are suffering from that complexity of symptoms known

*Clemens, Archiv. f. Heilkunde, 1854, p. 500.

†Billroth, Wiener Medic. Wochenschr. 1868, No. 47.

‡Dénonvilliers, Bulletin de l' Académie de Médec., Juin. Juillet, 1857, T. xxii.

as "shock," manifesting itself in mental apathy or unconsciousness, feebleness of the pulse, pallor of countenance, etc.

c. Bodily weakness.

It matters little whether this condition be the result of prolonged suffering, direct loss of blood, or venereal excesses. Paget,* in the case of a girl of dissolute habits, who died after the first few inhalations of chloroform, which was being given for the removal of a carcinoma of the vagina, attributed the death to the debilitated bodily condition resulting from her dissolute life. In confirmation of these observations are Clemens'† experiments on dogs, rabbits, guinea pigs, and also on large insects, which resulted in showing that those in which there had been previous immoderate sexual indulgence were more readily destroyed by chloroform and with smaller doses than those which had not been thus indulged.

d. Cardiac affections, and especially fatty degeneration.

A fatty condition of the heart, notwithstanding the negative results of an investigation in this direction by Kidd,‡ in persons who died during chloroform narcosis, must be regarded as an important factor in the causation of death under such circumstances. Sansom§ found it to exist in eighteen out of fifty-six such cases, and in the sixty autopsies tabulated by Kappeler‖ in sixteen there were various degrees of fatty degeneration of the heart. Regardless of this large percentage Kappeler holds a fatty heart to be relatively rather than absolutely dangerous, inasmuch as on the one hand some of those in whom this condition was found had previously taken chloroform without bad effects, and on the other hand he had never seen any symptoms of disturbance from the action of chloroform in amputations for senile gangrène, a condition in which atrophy and fatty degeneration of the heart are very common. This limitation of fatty degeneration of the heart to a sphere of but relative importance as a source of danger, is entirely proper, inasmuch as the very frequent occurrence of this condition, in slight degrees, would be liable, in an investigation of the causation of deaths from chloroform, to direct attention in wrong channels and lead to erroneous deductions.

*Paget, Lancet, October, 1853.

†Clemens, l. c., p. 504.

‡Kidd, British Medical Journal, 1862, Jan. 25, May 24.

§Sansom, Chloroform, its action and administration, London, 1866.

‖Kappeler, l. c., p. 121.

e. Chronic alcoholism.

It has not yet been determined how it is that inebriates present such abnormal reactions to the inhalation of chloroform as are so often noticeable in the operating room. Such individuals not only require much larger quantities of chloroform to bring about complete anæsthesia than are required in normal persons, but there also occur in them a high degree of excitation, manifesting itself in excessive muscular activity, shrieking and struggling and in unconscious attempts to leave the operating table. In the condition of relaxation which follows this stage of excitement there not infrequently occurs a state of collapse with stertorous breathing which may readily lead to a fatal issue. It is very natural to attribute these symptoms to the combined action of the alcohol and the chloroform, and attempts have been made to discover this action in different directions. Lefort is of the opinion that the organism weakened by the action of alcohol is unable to tolerate the chloroform, an explanation which is little more than a statement of the fact. According to Scheinesson* chloroform operates both to prevent the production of heat and to retard the bio-chemical processes in the body. Alcohol operates in the same way, and thus inebriates, through a combination of the action of these two agents, are more liable to unpleasant untoward symptoms and even to deleterious consequences. It is, however, difficult to understand how causes—a lowering of the temperature and a retardation of the chemical processes in the body—could operate in so short a time as intervenes between the commencement of narcosis and the beginning of sleep, to exert such excessive action. It would appear to be more natural to suppose that the material changes in the central nervous system in chronic alcoholism manifest themselves only in a higher degree and in a more deleterious manner in functional disturbances, than is the case in the ordinary excesses in alcoholic beverages. According to this view the collective abnormal symptoms are of either central or reflex origin.

According to the statistics collected from various authors the percentage of deaths from chloroform occurring among inebriates, varies from 10 to 13.

*Scheinesson, Untersuchungen über den Einfluss des Chloroforms auf die Wärmeverhältnisse der Organe und den Blutkreislauf. Dorpat, 1868 und Archiv der Heilkunde, Bd. X., 1869.

We have discussed in the foregoing the causes which, either singly or combined, result in death from chloroform, and have pointed out the symptoms under which it occurs. Fortunately, such deaths are relatively few—occurring about once in three thousand cases—and it is probable that by a closer investigation into the causation, a more favorable showing than this would appear. Doubtless the death rate would also be still further reduced through a correct knowledge of and attentive regard for the milder accidents which are observed in the majority of the cases of the administration of chloroform, and which, as was remarked at the beginning of this article, not infrequently precede death from chloroform.

To these occurrences belong the tonic spasm of the muscles concerned in mastication and the posterior muscles of the tongue, which frequently occurs during the stage of excitement. The tongue is thus drawn spasmodically backwards by means of the stylo-glossal and stylo-pharyngeal muscles, and presses down the epiglottis. In this manner there is caused a mechanical closure of the entrance to the glottis, which, if relief be not at once afforded, results in mechanical suffocation, with cyanosis of the lips, exophthalmus, etc.

Another unpleasant untoward effect is the vomiting which may occur at any stage of the action of chloroform. This nearly always occurs when the stomach is full, and may be so persistent as to continue for even twenty-four hours after recovery from the anæsthesia, and is usually accompanied by thirst, headache and mental depression. The entrance of the contents of the stomach into the air passages seldom occurs under such circumstances, inasmuch as the patient usually awakes at the commencement of vomiting. In the 101 cases of death collected by Kappeler, death occurred from suffocation in this manner in only two.

In rare cases jaundice and the discharge of the coloring matter of the bile in the urine have been observed as a result of the inhalation of chloroform.

The greatest attention is, however, demanded by the symptoms referable to the organs of respiration and circulation. As has already been stated, reflex apnœa may occur after the first few inhalations of the chloroform. There suddenly occur in such cases one or more pauses of greater or shorter length in respiration, or the inspirations become shallower and slower, or, finally, after a long,

jerking expiration, inspiration is entirely suspended. These conditions either spontaneously disappear or are readily relieved by skilled assistance. In the same manner irregularity or complete stoppage of the pulse, and pallor of the face, may also occur. These symptoms may also disappear spontaneously. In contrast with these is that group of symptoms which present under the name of chloroform syncope, in which the radial pulse suddenly disappears, the heart sounds become scarcely audible, the face assumes the appearance of death and respiration ceases. It is only in the rarest cases that restoration is possible under such circumstances.

Richet* noted another untoward effect of chloroform which is remarkable, however, only from a pathological point of view. During a normal narcosis there appeared an eruption of dark-red spots which spread over the whole body and which had the appearance of purpura hæmorrhagica, disappearing, however, under pressure of the finger.

The untoward effects of the external application of chloroform to the sound skin or mucous membrane, are of an interest quite equal to those following its inhalation. Following the rubbing in of chloroform upon the sound epidermis there occurs a smarting redness, and not infrequently there appears an urticaria-like eruption or an eczematous change of the skin, while vesicles may also result from its long-continued use. Applied to certain sensitive portions of the skin, as, for instance, the scrotum, chloroform causes such severe and persistent pain that the patient usually objects to its renewal. For this reason the method of treating orchitis recommended by Bouisson,† viz., the application of compresses wet with chloroform, is objectionable.

Chloroform applied to wounds and mucous membranes causes irritation of disproportionate intensity. When during anæsthesia it drops from the chloroform basket on the lips, it sometimes either produces fissures of the lips, or the mucous membrane is shed in pieces.

The treatment of chloroform accidents.—The disturbances of respiration and circulation are the first to demand energetic treatment. The mechanical closure of the glottis by the spontaneous

*Richet, Journal de la Société des Scienc. Médic. de Bruxelles, 1851.

†Bouisson, Annales des maladies de la peau Janvier, 1851.

falling back of the tongue or by spasmodic contraction of the posterior muscles of the tongue, is overcome by opening the mouth, if need be by means of Heister's speculum, and by forcibly drawing the tongue forward by means of a tongue forceps or a loop of thread, and cleansing the mouth of mucus. In many cases the embarrassment to the entrance of air may be overcome by the more simple manipulation of the lower jaw, after the method described by Heiberg.* This is best accomplished by the operator's standing behind the recumbent patient, placing both thumbs on the symphysis of the lower jaw, pressing the second joint of the bent index finger behind the posterior borders of the ascending rami of the jaw, thus holding the entire bone firmly between his hands and then drawing it forcibly forward. To accomplish the same object, Kappeler, standing before the patient, places his thumbs close beside his nose on the anterior border of the upper jaw and with the hooked index fingers, formed by bending the distal phalanges, placed behind the angles of the lower jaw, draws the bone forward. By this means both the tongue and the os hyoides are drawn forward and the epiglottis, which is drawn with them, is raised up.

If, notwithstanding the fact of unobstructed entrance of air into the lungs, disturbances of the respiration and circulation supervene, with simultaneous change in the color of the patient's face, the chloroform should be forthwith discontinued and a free supply of fresh air provided, and should anæsthesia not be complete, as evinced by response through reflex movements to external irritation, the cold water douche or the injection of cold water into the nasal cavities, and the use of irritant inhalations, as of ammonia, carbonate of ammonia, etc., should be resorted to. As Billroth,† however, very truly declares, no time should be wasted in these measures in complete anæsthesia. They are of no service under such conditions and resort must at once be had to artificial respiration.

A number of methods of effecting artificial respiration have been proposed:

1. Direct inflation from mouth to mouth, in which method expiration is assisted by compression of the lower portion of the thorax,

*Heiberg, Berliner Klin. Wochenschr., 1874, p. 449.

†Billroth, Wien. Medic. Wochenschr., 1868, p. 795.

and for the completion of which the nostrils must be closed. In this method, as Billroth has observed, a portion of the air blown in finds its way into the stomach.

2. Inflation by means of a bellows. Plouviez* introduced the nozzle of a bellows into one nostril or into the throat, and suddenly expressed a current of air into the lungs. At the same time the breast and the abdomen were alternately compressed.

3. Inflation through a laryngeal catheter. Should it be impossible, owing to spasm of the posterior lingual muscles and the upper pharyngeal muscles, to introduce the catheter, tracheotomy will be necessary and air introduced through the tracheal canula by the mouth or bellows.

4. Marshall Hall's method, in which the patient is regularly several times a minute turned on his back and on his side, pressure being made on the back at each turn.

5. Galvanization of the phrenic. The moistened positive electrode of a constant battery or interrupted induction apparatus, is placed over the phrenic nerve in the neck, over the scalenus muscle, and the negative electrode over the præcordial region under the border of the ribs, or both poles are placed on the neck, one on each side, at the outer border of the sterno-cleido-mastoid muscles.

6. Allowing the head of the patient to hang down, according to Nelaton, or suspending him by his feet, after the method successfully adopted by Spoerer† in one case.

7. Acupuncture or electro-puncture of the heart. This was resorted to by Hüter,‡ as a dernier ressort, but without success in a case of arrest of the heart-beat. He plunged one needle two inches in length into the fourth intercostal space at the edge of the sternum, to the depth of three quarters of an inch to an inch, and a second nearer the nipple and somewhat lower down.

The occurrence of one or several fits of vomiting during anæsthesia, or on awaking from it, seldom demands therapeutic interference. Should it, however, become more frequent, small pieces of ice or champagne should be given. Usually the application of cold compresses over the stomach suffices to allay it.

*Plouviez, Journal de la Soc. des Sciences médic. de Bruxelles, 1857, p. 14.
†Spoerer, Petersburger Medic. Zeitschrift, 1866, p. 110.
‡Hüter, Berliner Klin. Wochenschr., 1865, p. 486.

IODOFORMUM.

Aside from the odor due to its elimination, there have as yet been no untoward effects observed from the employment of iodoform, other than such as are referable to the central action of the drug. After the anæsthetic or hypnotic action of this drug had been indicated by Italian authors, Binz* showed that the effect was due to a liberation of iodine in the system. "As a yeast-cell when touched by iodine no longer decomposes sugar, and a white corpuscle no longer throws out processes, so is the peculiar function of a brain cell under such circumstances held in abeyance; it is no longer susceptible to external impressions, and ceases to generate impulses for its centrifugal processes. It sleeps, should the effect caused by the iodine be reparable; should the structure be destroyed by the iodine, it dies."

An illustration of the correctness of this deduction is afforded by several cases reported by Oberlænder,† among others, in which untoward effects of a central nature followed the employment of iodoform. A female affected with gummy tumors took 42 grammes (ʒ xss) of iodoform, in the form of pills, in the course of 80 days. There occurred at the end of this time vertigo, a sensation of weakness and double vision. These symptoms continued two and a half days. In spite of the suspension of the pills, she began to vomit and fell into a deep sleep, from which she was aroused only with difficulty. For several days this sleepiness alternated with excitement, incoherence of speech, a feeling of anxiety and twitching of the muscles of the face and trunk. It was not before the twelfth day after the onset of these symptoms that she could stand alone and walk a short distance.

The second case was that of a person who had taken five grammes (gr. lxxv) of iodoform, in pills, in the course of seven days, for ulceration of the throat. Somnolence supervened, the gait became difficult and uncertain, and there was headache over the entire circumference of the head. After this condition had lasted for a day, there set in a comatose condition, which lasted for five

*Binz, Archiv. f. Experimen. Pathologie u. Pharmakologie. Bd. viii., p. 310, u. Bd. viii., p. 159.

†Deutsche Zeitschrift f. pr. Medicin, 1878, No. 37. Refer. in Archiv f. Dermatologie u. Syphilis, 1879, p. 372.

days, the patient responding promptly, however, to external irritation and making motion as if warding it off, and swallowing nourishment. The urine showed a distinct iodine reaction. It was not until after fourteen days after the appearance of these symptoms that the patient could be pronounced cured. The liability of confounding these cases with cerebral syphilis is slight, inasmuch as there is no improvement in the latter from the expectant plan of treatment.

Connected with the extensive employment of iodoform in antiseptic dressing, as also as a specific in localized tuberculous processes as it is now employed in surgery, a series of untoward effects, at times dangerous and even fatal, have been noted. The majority of these are traceable to the injudicious use of the drug. Large cavities of wounds, joints, etc., have been and are still, packed with this substance and even from 100 to 200 grammes (℥ iij to ℥ vj) has been introduced into the cavity of the abdomen. It is not to be wondered at that the deleterious action of iodine should thus be manifest in the most varied organs and systems. In some cases the temperature is raised to 41° C. (105.8° F.), the pulse to 150 per minute, vomiting occurs, the appetite is diminished, the patients become languid, complain of dizziness, mental confusion, are incapable of either mental or physical exertion and usually fall into a lethargic condition. Following this condition, according to Henry,* paralysis of the sphincters, disturbances of speech and finally death may suddenly occur. Should even a certain degree of toleration have been secured through several weeks' use of the drug, death may occur with mental clearness but with aseptic fever, even should the use of the drug in the meantime have been discontinued.

The most disturbing, and through their relative frequency and the suddenness of their onset, the most dangerous forms of intoxication, are, as Schede† has declared, on the basis of his own observations, are the disturbances of the cerebral functions, whether these are due to acute meningitis or to actual mental disease (melancholia, great depression of spirits, etc.), which occur, and which, even when the iodoform has been discontinued, may lead to a fatal issue.

These results, as L. Lewin‡ has declared, compel us to look to

*Henry, Deutsche Médic. Wochenschrift, No. 34, 1881.
†Schede, Centralbl. f. Chirurgie, No. 3. 1882.
‡L. Lewin, Berl. Klin. Wochenschrift. No. 42, 1882.

other causes than the doses in which the drug has been employed, and above all to have a regard for the individuality of the patient.

The desired therapeutic end may be secured by much smaller and non-toxic doses by insufflating the drug in a finely powdered condition into the cavity of wounds, or by dusting it on wounded surfaces. In the case of existing fistulæ iodoform pencils may be introduced for their antiseptic effect, and in situations to which it is impossible to apply the solid substance, the iodoform may be applied by means of volatilization with steam. In cases in which untoward effects occur even in connection with these means of the administration of the drug, the cause must be referred to the idiosyncrasy of the individual. This idiosyncrasy seems to be peculiarly marked in the case of females.

The exhibition of large quantities of iodoform may, as observed by Falkson,* cause the drug to play the part of a foreign body; it may become incorporated with the newly formed connective tissue in which it may remain encapsuled after the subsidence of the healing process. In such cases, however, it generally gives rise to an iodoform abscess, showing itself in a circumscribed swelling, with pain on pressure and redness of skin. An incision causes the expulsion of pure iodoform, with occasional slight admixture with mucus. The exhibition of iodoform in the form of crystals is particularly favorable to the formation of such abscesses.

METHYLENI BICHLORIDUM.

Since 1867, when Richardson first recommended the bichloride of methylene, or chloromethyl, as an anæsthetic, this drug has been extensively employed, it being said to be preferable to chloroform in that its use is attended with less danger and is accompanied by but slight untoward effects. It has, however, been established in course of time that this substance has no special advantages over chloroform and is scarcely less dangerous. Holländer,† who employed it in the extraction of teeth, found it necessary in one case to administer nearly 30 grammes (℥ j) to destroy sensation, after which he observed a state of excitement, severe fits of vomiting, and a condition of confusion of the head which continued for

*Falkson, Archiv. fur Chirurgic Bd. X.

†Holländer, Berliner Klin. Wochenschrift, 1867, p. 49.

upwards of an hour after the cessation of anæsthesia. Hegar and Kaltenbach* noticed asphyxia after the inhalation of the bichloride of methylene, and when the drug was administered by means of the wire basket instead of Junker's apparatus, it caused excoriation of the lips and cheeks.

But in addition to these slighter accidents, fatal consequences have followed the exhibition of the drug. These occur either suddenly, without disturbance of respiration or change in the color of the face, or the breathing becomes gasping, the pulse at the wrist small and fluttering, the color of the face pale or livid, and death occurs with complete arrest of the pulse and no convulsions. It should be mentioned here that a more recent examination of a preparation known as bichloride of methylene, imported from England, shows it to present nothing in common, except the name, with the methylene chloride; that it consists much more largely of chloroform, which may, by the addition of alcohol, be brought to nearly the specific gravity of the methylene bichloride.

ETHYLIDENI BICHLORIDUM.

The chloride of ethylidene, recommended as an anæsthetic and occasionally employed clinically for this purpose, is a fluid which boils at 60° C. (140° F.) and produces prompt and easy anæsthesia with regularity of the pulse and respiration. The occurrence of a death during anæsthesia induced by this agent, has, however, prevented its further trial.

ETHER SULPHURICUS.

Sulphuric ether, like chloroform, causes by its inhalation, a series of accidents which are either of a transitory nature or may be attended with fatal consequences. The transitory symptoms are associated with persistent vomiting, which occurs not only during the anæsthesia but continues also after the operation, to be followed by explosive coughing. The latter occurs, probably, in consequence of the accumulation of saliva in the air passages, due to the

*Hegar u. Kaltenbach, Operative Gynækologie, 1874, p. 25.

increased salivation which always occurs during the anæsthetization.

The threatening symptoms are referable to the respiration and the circulation. Pallor or cyanosis of the face occur, the respiration at the same time becoming irregular or ceasing entirely, and the pulse becoming small and finally imperceptible. Cases are reported in which artificial respiration, drawing forward the tongue, etc., were successful in effecting restoration even after this threatening condition had set in. Should, however, the mechanico-therapeutical means against these disturbances not be at once resorted to, death occurs suddenly, the respiration and pulse ceasing simultaneously, or the latter outlasting the former for several minutes. In the majority of cases reported by English authors, death occurred without any premonitory symptoms. In a few there occurred violent muscular excitement, cyanosis or turgescence of the face, dilatation of the pupil or labored breathing. Only one fatal accident has occurred in each 30,000 anæsthetizations by ether.

The rules governing the procedure against these accidents are the same as those which are to be observed in chloroform syncope. As a prophylactic measure the head must be raised so as not to afford the saliva an opportunity to flow into the air passages. Regard must also be had, as in the case of chloroform, to the degree of concentration of the vapor, and that the preparation employed be perfectly pure.

The habitual use of ether, as was noted in the case of a so-called "ether-breather," observed by Ewald,* gives rise to general lassitude, weakness, muscular tremor, and a peculiar, disagreeable odor of the body.

AMYLI NITRITUM.

The amyl nitrite, a product of the action of nitric acid on amylic alcohol, was held during the first years of its employment, providing it contained no deleterious by-products, such as hydrocyanic acid and nitric acid, to be a harmless substance, productive of no disturbing symptoms. Later, however, untoward effects referable to the functions of various organs have been frequently

*Ewald, Berliner Klin. Wochenschrift, 1875, p. 133.

observed to follow its use. The occurrence of these is dependent on the individuality of the person, but may also occasionally occur in those who are accustomed to the inhalation of the drug.

Of the special organs of sense that of sight is most frequently affected by its use. The subjective sensations of color which it produces are not, as Schrœter* found in several patients, alike in all cases, being only occasionally very distinct in many, and not exactly alike at each inhalation. They consist in their typical form, according to Pick,† of the appearance of an intensely yellow halo around any fixed point upon a bright background. The yellow circle is again surrounded by a bluish violet border. This symptom is probably nothing more than the projection of the macula lutea, and the bluish-violet border its complementary color. The patients treated by Sander,‡ with the nitrite of amyl, declared of their own accord, that everything seemed yellow to them for some time. It could not be accurately determined in these cases whether this was owing to the yellow color of the portion of the field of vision corresponding to the macula lutea. This yellow vision disappears only after some minutes, gradually becoming paler. Schrœter noticed also an impairment of the acuteness of vision. Patients who had inhaled the amyl nitrite for some time found it impossible, for instance, to distinguish clearly the figures of a large clock, they having a blurred appearance. Normal acuteness of vision returned with the suspension of the drug.

Abnormal effects on the central nervous system have been but rarely observed. Veyrières § observed in his own case, after the continued inhalation of the drug, vertigo and stupor lasting from six to eight minutes and followed by headache of two hours' duration. In some cases of mental aberration Schrœter noted delirium of the senses, or increase or diminution of the same, during the inhalation of the drug, and Bourneville‖ has reported similar cases. He observed the occurrence of violent headache, vertiginous feeling, and, in hysterical persons, illusions of sight in connection with the yellow vision, as results of the employment of the nitrite of amyl.

Following the inhalation of this agent, and to a certain degree

*Schröter, Zeitschrift f. Psychiatrie, Bd. 32, 5, p. 527.
†Pick, Centralbl. f. die Medic. Wissenschr., 1873, p. 866.
‡Sander, Medicin. psycholog. Gesellsch. zu Berlin, Sitzung vom 4, December, 1874.
§Veyrières, Virchow-Hirsch's Jahresbericht, 1875, I., p. 481.
‖Bourneville, Gazette Médicale de Paris, 1876, No. 13.

occurring as an after-effect, Sander observed sudden profound collapse characterized by fainting, falling, pallor of countenance, a small pulse and a cold, clammy sweat. Samelsohn* also describes a case in which a patient, while under the full effects of the nitrite of amyl, drew a few deep spasmodic breaths, became chilly and was covered with a cold sweat; the pulse became small and thready and extraordinarily slow, and while consciousness was impaired it was still retained. Urbantschitsch†, too, notes the fact that in some cases the inhalation of even two drops of the nitrite of amyl may cause collapse, with paresis or serious vertigo and embarrassment of respiration.

In connection with the other untoward effects the statement of Bourneville is noteworthy, that following the inhalation of the nitrite of amyl there frequently occur trembling of the lips and difficulty of chewing. Urbantschisch observed after its use dryness of the mouth, which lasted for from twelve to twenty-four hours. Occasionally there first occur, instead of redness of the face, palpitation of the heart, pressure in the head and ears and irritation of the throat. Veyrières also observed the latter symptom, while Ladendorf‡ noticed on two occasions, during a four weeks' course of the amyl nitrite, the occurrence of a violent, dry spasmodic cough. Some other authors have also reported distressing nausea and vomiting as results of the repeated inhalation of the drug.

In using the nitrite of amyl care must be taken that the preparation employed does not present an acid reaction. Unless a few small pieces of burnt chloride of calcium or a little magnesia have been added to it, a preparation of amyl nitrite, originally neutral, may undergo decomposition and generate nitric acid on standing a length of time. Hydrocyanic acid is easily detected by shaking the nitrite of amyl with water, and testing the latter for Prussian blue.

*Samelsohn, Berliner Klin. Wochenschrift, 1875, p. 349.
†Urbantschitsch, Wiener Medic. Presse, 1877, 8 u. ff.
‡Ladendorf, Berliner Klin. Wochenschrift, 1874, p. 539.

EVACUANTS.

I.—PURGATIVES.

OLEUM RICINI.

In many persons there is an unconquerable repugnance to castor oil, and when the oil is taken by such it frequently causes nausea and vomiting. The latter occurs also should the oil have lost its freshness and free fatty acids have formed in it. As means of disguising the disagreeable, peculiar fatty taste of castor oil and to render it more palatable, numerous vehicles, such as wine, brandy, milk and coffee, have been commended. Starke* recommended to this end that the oil be converted into a thick, dough-like paste, with sugar (1:3) or compound liquoric powder (1:3), and then incorporating this with powdered cinnamon or some other corrective.

ALOE.

As an accompaniment of the special action of aloe, viz., ordinarily soluble, non-watery stools with moderate griping, there not infrequently occur, in addition to a sensation of warmth and pressure in the region of the stomach and frequent eructations, a congestive condition of other abdominal organs, as the kidneys and uterus. Through such action pre-existing hæmorrhages, chiefly of the latter organ, may be aggravated to a threatening degree. Larger doses of aloes, given either in substance or in the form of extract, are also said to have been abortifacient. Women under such conditions complain of pain in the region of the kidneys and uterus, and of a feeling of weight in the pelvis.

Should an aloetic preparation be employed for a length of time, there occurs, in consequence of the persistent congestion of the descending colon and rectum, dilatation of the hæmorrhoidal veins

*Starke, Berliner Klin. Wochenschr, 1879, p. 232.

which may eventually give rise to hæmorrhoidal tumors. It is however, doubtful, in view of the numerous other uncontrollable conditions which give rise to this affection, whether the statement made by Fallopius* be true, that out of a hundred persons who make habitual use of aloes ninety are attacked by hæmorrhoids. Elderly, and weakly young persons manifest a special predisposition to such action of aloes.

FRUCTUS COLOCYNTHIDIS.

Colocynth belongs to the drastic purgatives, which probably exert their effects through a direct irritation of the mucous membrane of the intestines. For this reason, and particularly when the digestive tract is in an irritated condition, the stools caused by colocynth are accompanied by severe pain and tenesmus, and may even be mixed with blood.

TUBERA JALAPÆ.

Like most other resins and substances containing resins, which owe their purgative action to direct irritation of the intestinal tract, jalap root, which is operative only in the presence of bile or biliary salts, usually causes abdominal pains and borborygmi. Nausea occasionally manifests itself as an evidence of gastric irritation, and vomiting may also occur. Large and frequently repeated doses may give rise to catarrhal inflammation of the gastro-intestinal mucous membrane.

GAMBOGIA.

While small doses of gamboge ordinarily give rise to no peculiar untoward effects, there still occur in some persons, even after 0.1—0.2 gramme (gr jss—gr iij) abdominal pains, vomiting and distinct increase in the quantity of urine.

HERBA GRATIOLÆ.

Gratiola, formerly extensively employed as a purgative, causes

*Fallopius, Opera omnia. De Medicam. purg. simpl. Francofurti, 1600.

according to numerous old writings on the subject, even in doses of 0.5—1.0 gramme (gr viiss—gr xv), given even in the form of powder or decoction, instead of purgation, nausea and vomiting, or, in addition to these, salivation, burning in the urinary tract, anorexia, and, as Bouvier* observed in the case of a woman in whom it was administered in an enema, nymphomania. Probably the age of the drug, and its percentage of gratiosolin, the active principle of gratiola, have much to do in determining the occurrence of the symptoms named.

FLORES SULPHURIS.

Sulphur, which has been extensively prescribed, in its various chemical combinations, as a purgative in thoracic affections and in chronic metallic poisoning, may, particularly when the digestive tract is not intact, readily excite gastric and intestinal irritation and digestive disturbances. In the presence of the alkaline intestinal juice it is partially transformed into an alkaline sulphate, and as this is decomposed by the carbonic acid of the blood and the tissues into absorbable sulphuretted hydrogen gas, the skin and the expired air usually smell of this gas. In larger doses this drug may, according to Wibmer,† give rise to a miliary eruption.

During the external application of sulphur ointment there occurs, in some persons, an artificial eczema, which soon disappears with the suspension of the drug.

OLEUM TIGLII.

Croton oil, when administered internally, frequently gives rise, in different degrees in different persons and in addition to its drastic purgative action, to an irritative, burning taste in the mouth, dryness and burning in the throat, eructations, nausea and colicky pains in different parts of the abdomen.

As a derivative, applied externally to the skin, there occurs after one or two applications, an erythema accompanied by itching and pain and slight fever, and upon this there appear, sometimes discrete and sometimes confluent, hard vesicles with serous contents, which in a day or two become purulent—and then burst, or there

*Bouvier, Gazette de Santé Août. 1816.
†Wibmer, Wirkungen der Arzneimittel, V., p. 276.

appear at once a large number of maturated pustules upon which crusts form within twenty-four hours. There not infrequently occur, secondarily, particularly on the scrotum, according to Wibmer*, herpetic eruptions, due, perhaps, to accidental contact of the oil, but perhaps also to its positive absorption. The former is the more likely, inasmuch as such eruptions have never been observed as a result of the internal exhibition of the drug. Tartar emetic, after whose external application similar secondary eruptions have also been observed on the genitals, differs from croton oil in that when given internally it may also give rise to these exanthems. Experiments on animals have shown that the external application of croton oil causes albuminuria, and that too without regard to the painful eczema, and without the causation of any appreciable inflammatory change in the kidneys. The possibility of such changes in the urine of human beings has not, as yet, been recognized.

According to Langenbeck,† the endermic introduction of croton oil gives rise to phlegmonous inflammation and suppuration.

The above-mentioned skin affections disappear with slight desquamation in from three to eight days after the suspension of the drug, leaving only a pale yellow discoloration at the seat of the affection.

II.—EMETICS.

ANTIMONII ET POTASSII TARTRATIS.

It is known that the external application of tartar emetic, either in solution or ointment, causes both eczema (papules, vesicles, œdema) around the orifices of the glands, as well as extensive pustular disease (ecthyma antimoniale) of the skin. The derivative method of treatment, to which end tartar emetic is still occasionally employed, causes intense pain to the patient. Usually only a simple inflammatory irritation is aimed at, but instead of this there is apt to occur extensive destruction of tissue. Particularly in the application of the so-called "pox salve" to the head to combat certain mental diseases, such as dementia paralytica, there readily occur deep, excavated ulcers, with occasional exfoliation of bone at the

*Wibmer, l. c. I., p. 215.

†M. Langenbeck, Die Impfung der Arzneikörper, Hannover, 1856, p. 84.

bottom of the lesion. Among the older reports bearing on this subject, should be mentioned that by Jacobi*, who, in the year 1819, witnessed in several persons whose entire scalps had been anointed with tartar emetic ointment, perforation of both lamellæ of the parietal bones, resulting from necrosis following the inunction. In view of such facts it is certainly not superfluous to mention that Hebra long since denounced such treatment as a "useless, injurious procedure, and occasionally even dangerous to life."

The internal administration of tartarized antimony as an emetic, either alone or in combination with ipecacuanha, as also the employment of other preparations of antimony, is sometimes followed, especially in children, by a condition resembling collapse, owing to the very pronounced property of antimony in causing a lowering of the frequency and force of the heart beat. It is recommended, for these reasons, that analeptics, such as wine, coffee, etc., be given after each emetic action of the drug. All those dangerous symptoms and even fatal results which have been reported as following the longer or shorter administration of the drug, even in small doses and to adults, are referable to the same cause. Doubtless the individuality of the patient plays an important part in such cases. Thus Falot† reports three cases in which, after from one to three small doses of tartar emetic, there occurred, in addition to vomiting, delirium and spasms, such prostration of the vital powers that life was saved only through the energetic use of stimulants. Beau‡ made an observation which was quite analogous, two fatal cases occurring after the exhibition of small doses of antimony. In these cases also the symptoms from the first were those of pronounced debility—a very small pulse, general cyanosis and emaciation of the face. The prostration increasing and the extremities being cold, death ensued. Although tartar emetic is now no longer as extensively employed as formerly, it is employed with sufficient frequency as an emetic and expectorant to justify this reference to the possibility of deleterious consequences from its use.

Its exhibition should be strictly interdicted in persons suffering

*Jacobi, Damerow's Zeitschrift f. Psychiatrie, Bd. XI., p. 369, Ref. bei Schuchard, Arzneimittellehre, Braunschweig, 1858, p. 226.

†Falot, Union Médicale 1852, p. 245.

‡Beau, Bulletin de Thérapeutique, Sept. 1856.

from the slightest pathological condition, such as catarrh, etc., of the intestinal tract, inasmuch as either its external or internal administration in such cases always excites inflammatory irritation and even deeper lesions of the mucous membrane of the stomach and intestines. This disturbance, after the external application of the drug, occurs, as demonstrated by Radziejewski,* through the elimination of the metal through the stomach and intestines. This inflammatory irritation is also, doubtless, the cause of the vomiting. This is induced by reflex irritation of that part of the central apparatus which controls the act of vomiting. Occasionally excessive vomiting occurs.

The caustic action of tartar emetic, as also that of other combinations of antimony, Kermes mineral, for instance, occasionally manifests itself, during the internal exhibition of medicinal doses, in pustules and vesicles in the mouth, throat, œsophagus and even in the larynx. Lænnec† held these symptoms to be secondary and due to a saturation of the body with the drug. Falck,‡ on the other hand, declared this action to be purely local and due to the exhibition of the drug in solution, no instance of any of the changes mentioned having ever been observed to follow its administration in pill form. Although we may not be able to admit the hypothesis of the saturation of the system with tartar emetic, we must, nevertheless, concede the possibility of the secondary occurrence of the changes mentioned as an effect of the antimony circulating in the blood, and particularly so because of the fact that affections of the skin and mucous membrane have been seen in parts with which, primarily, the drug never came in contact. Thus it has been established, through numerous observations, that not infrequently, and without the drug's having been conveyed by the fingers from the original seat of application, that secondary pustular eruptions occur, particularly on the genitals and inner surfaces of the thighs, several weeks after the inunction. In addition to this there have been many cases reported in which pustular eruptions have occurred by preference on the parts mentioned, and also on other parts, after the internal exhibition of tartarized antimony. Thus Imbert-Gourbeyre§ adduces an observation of

*Radziejewski, Archiv f. Anatomie u. Physiologie 1871, p. 472.
†Lænnec, Gazette des hôpitaux 1853, No. 6.
‡Falck, Canstatt's Jahresbericht uber die gesammte Medicin 1853, V., p. 148.
§Imbert-Gourbeyre, Gazette Médicale de Paris 1861, pp. 3, 17 u. ff.

Gohlius'* in which, after a large dose of antimony, there occurred a red eruption over the entire body. Bœck† also saw a similar occurrence after the administration of 0.6 gramme (gr. jx) of tartar emetic during 36 hours, and Helbert‡ reports a similar case. In explanation of this phenomenon, there are, as Hermann pointed out, two possibilities. Its cause must reside either in an inflammatory irritation acting on the peripheral nerves, and thus exciting reflex inflammatory changes in the vessels, or in a direct action on the vessels themselves. Engorgement of the capillaries of the skin and exudation thus occur, and finally the formation of pustules. It is also possible, however, for the glandular organs of the skin to suffer inflammatory change through the direct action of the drug.

The slightest forms of antimonial eruption demand no therapeutic interference. Extensive ulcerations are to be treated on the general principles governing the treatment of wounds. The gastric disturbances demand treatment, particularly should there be oppression and pain in the region of the stomach, and should but a short time have intervened between the exhibition of the antimony and the occurrence of these symptoms. To this end the stomach should be washed out, opiates or other narcotics, in small quantities, being added to the fluid employed. Should there be excessive vomiting, the vegetable astringents, tannin, decoction of cinchona, etc., should be resorted to, inasmuch as in such cases antimony is probably present in the stomach, and this forms such combinations with the drugs named as are either but slightly soluble or entirely insoluble.

RADIX IPECACUANHÆ.

Ipecac, now but seldom applied internally for its irritant effect on the skin, causes, as noted by Bazin, § when applied in the form of an ointment (1: 2 of lard), after the second or fourth inunction, a papular eruption—without disturbing the underlying corium. At first there is a diffuse redness with burning, and upon this there appear slight elevations. The number and size of these latter increase, with intense itching, while the intervening skin may regain

*Gohlius, Medicin. practic., clinic. et forensis. Lipsiæ, 1735.
†Bœck, Preussische Vereinszeitung 1843, No 8.
‡Helbert, De exanthemat. arte factis, Göttingen, 1844.
§Bazin, Leçons sur les affections cutanées artificielles, Paris, 1862, p. 106.

its normal appearance. They finally become quite large and red, remain distinct, and disappear under pressure of the finger. After suspension of the inunction the eruption begins to disappear after a time—from one to two weeks—without desquamation or leaving any scars. The pruritus continues until complete disappearance of the eruption. According to Delioux* an ipecac ointment may give rise to pustules with depressed centres, like those caused by tartar emetic, with this difference, however, that it leaves no scars like the eruption caused by the latter.

The repeated internal administration of small doses of ipecac may, through the local action of the drug, give rise to gastric and intestinal catarrh, with its natural consequences, anorexia and diarrhœa. The latter occurs most frequently when vomiting is not excited. The passages are then less abundant, usually mucous or bilious and slimy, and frequently tinged with blood. According to Arnold† ipecac not infrequently manifests differences in its effects. Occasionally vomiting follows 0.6 gramme (gr. jx), while in other cases 2.4 grammes (gr. xxxvj) causes no such action. The cause of the difference resides partially in the individuality of the patient, partially in the activity, the origin and the age of the root. Emetin, the alkaloid of ipecac, is more uniform in its action, but it, also, is not free from untoward effects.

III.—DIURETICS.

BULBUS SCILLÆ.

Squill and its active principle, scillitin, in addition to their diuretic property, occasionally in small medicinal doses give rise to nausea, and should it be given in such small doses for any considerable length of time, as in dropsical conditions, vomiting and a serous diarrhœa with griping may supervene. Inasmuch as it fails of its diuretic action after a time, the doses are usually enlarged. Following such increase the symptoms as described may become aggravated, and irritation and burning of the throat, colicky pains, pain on voiding urine and bloody urine may

*Delioux, Gazette de Paris 1852, No. 6 u. ff.

†Arnold, Das Erbrechen und die Wirkung der Brechmittel, Stuttgart, 1840.

occur. These symptoms are the expression of a local irritant action of the drug on the portions of the mucous membrane with which it comes in contact. As a reflex action from the stomach a diminution in the frequency of the pulse is observed.

RADIX SARSAPARILLÆ.

Following the exhibition of large doses of sarsaparilla root, gastric uneasiness, nausea, inclination to vomit, anorexia and general debility are frequently observed. These symptoms are identical with those which have been noticed after the therapeutical employment of smilacin, the active principle of the root.

FOLIA TOXICODENDRI.

The officinal fresh leaves of poison-sumach contain a yellowish-brown milky juice, which is also found in the tincture of the rhus toxicodendron. This drug has been but seldom employed in recent times. It is, however, still necessary to mention the fact that the fresh leaves, as also the tincture, when given in doses within the maximum limit, may cause in certain persons pain, gastro-enteric symptoms, as also vertigo, deafness, delirium, anæsthesia and a paralytic condition. In addition to these there occur after the external application of the fresh leaves or the extract, violent itching, an erysipelatous redness and swelling of the skin, and also a vesicular, rubeola-like, intensely itching eruption, which disappears only after several days, with desquamation. The same symptoms are said to be caused by the emanations of the living plant.

IV.—EXPECTORANTS.

AMMONII CHLORIDUM.

Small doses of sal ammoniac introduced into the stomach cause no symptoms of disturbance. The prolonged use of doses of 1 to 2 grammes (gr. xv. to gr. xxx.) may, however, cause derangements of digestion and loss of appetite. The daily administration of quanti-

ties of 4 to 8 grammes (3 j. to 3 ij.) was observed by Jacquot* to cause, in addition to nausea and vomiting, diarrhœa and colic. It seems that the occurrence of these untoward effects is dependent on individual circumstances. The continued use of the drug in moderate doses usually gives rise to constipation, which is due to an atonic condition of the intestines.

ANTIMONII SULPHURETUM.

Owing to its insolubility in water and dilute acids the sulphuret of antimony, favorably regarded as an expectorant and resolvent, is not absorbed from the stomach. As was demonstrated by the experiments of L. Lewin,* it is, however, partially soluble in the alkaline juices of the intestines, and may thus, as practical experience teaches, give rise to the full effects of antimony, as manifested by the occurrence of vomiting and diarrhœa. The intensity of these untoward effects is dependent on the quantity of the drug dissolved in the intestines. It varies, however, with the degree of fullness of the stomach, as when the stomach is full the free drug which is not absorbed is carried with the contents into the intestines, and thence discharged with the fæces. According to this the untoward effects are most intense when the stomach contains the least food.

RADIX SENEGÆ.

The older literature contains isolated statements regarding the untoward effects following the use of senega. Thus in individual cases doses of 1 to 1.5 gramme (gr. xv. to gr. xxiii.) are said to have caused irritation and burning in the throat, salivation, gastric oppression, nausea and vomiting, and loss of appetite. These symptoms were followed by colicky pains and diarrhœic discharges. More recently attention has been called to the fact that occasionally a drug is sold as senega by reputable trade houses, which neither produces the effects of senega nor is botanically identical with it.

*Jacquot, Schuchardt's Arzneimittellehre, Braunschweig, 1858, p. 390.
*L. Lewin, Virchow's Archiv. Bd. 74.

V.—ANTIPARASITICA.

BALSAMUM PERUVIANUM.

In contrast with other balsamics Peruvian balsam has heretofore been seldom reported to cause untoward results. Recently, however, Mœgling* has reported the occurrence of an urticaria which lasted for four days, as the result of a single inunction with the balsam of Peru. Having one evening anointed himself on the arms, shoulders and breast, with about 8 grammes (ʒ ij.) of the balsam, for the cure of scabies, he was attacked with heat and uneasiness and also a burning sensation in the lungs with fits of coughing. On the following morning there appeared on the inner surface of the knee and on the shoulders a redness of the skin in patches, accompanied by intense pruritus. The itching disappeared during the course of the day, but reappeared towards evening. It appeared in closely disposed wheals situated on the thighs, sides of the abdomen, arms and shoulders. Simultaneously he experienced chills and nausea, without elevation of temperature. It was only after two days and following occasional inunctions of lard, with relief of the local and constitutional symptoms, and after the urticaria had in turn also attacked the face, neck, back, forearms, legs and dorsal surface of the feet, that Mœgling relieved himself by means of a bath, and by removing a woolen undershirt which he had worn for four days.

The congestion of the lungs may, according to Mœgling, have been due either to absorption of the drug by these organs, or, seeing that he had been suffering for some time from bronchitis and hæmoptysis, it may have been the expression of a deleterious action on the place of least resistance."

Less extensive eczematous eruptions of the skin are occasionally observed as results of a local irritant action of the Peruvian balsam —perhaps only when an inferior quality is applied—on parts to which it has been applied for the relief of scabies. Such an eruption may cause the disease to be suspected long after the itch-mites have been destroyed.

*Mœgling, Berliner.Klin. Wochenschr., 1880, p. 557

STYRAX LIQUIDUS.

Unna* observed albuminuria in patient suffering from scabies, and being treated with styrax ointments (styrax, rapeseed oil, of each 10 parts, and spirit 1 part). It occurred in nine out of 124 patients thus treated. A relatively large quantity of albumen quickly appeared and as quickly disappeared. Unna maintains that the tolerably large amount of balsamic substance which is absorbed by the skin is the cause of the albuminuria. The passage of substances of higher atomic weight through the walls of the renal capillaries is said to make them capable also of allowing albumen to pass through.

RHIZOMA FILICIS.

Ext. Filicis Maris Æthereum.

The root of the male fern, or its extract, administered in extraordinarily large doses for the expulsion of the tapeworm, has a disagreeable, irritating taste and occasionally gives rise to gastric pains, nausea, vomiting, diarrhœa and abdominal pains. It is to be suspected that the uncertain strength of the preparations employed is responsible for these symptoms.

CORTEX RADICIS GRANATI.

The administration of pomegranate root bark in doses such as are ordinarily exhibited for the expulsion of tapeworm, and particularly when the intervals between the doses are too short, is frequently productive of nausea, vomiting, abdominal pains and diarrhœa. Not infrequently there also occur vertigo, a feeling of weakness and occasionally trembling of the limbs. In weakly persons the continued vomiting may result fatally. The vomiting is, however, peculiarly obstinate when the pomegranate root bark has been given in immoderate doses, of say 300 grammes (℥ j x ss) as recommended by Bettelheim. Such doses are never permissible. According to Mérat, the bark is also a diuretic. These symptoms soon

*Unna, Virchow's Archiv, Bd. 74.

disappear with the suspension of the drug. These different effects are dependent on the age of the preparation, the fresh root alone having any curative effect. In the use of a reliable preparation the necessary doses are smaller, and inasmuch as the effects soon follow the untoward effects are also of less frequent occurrence and of shorter duration.

SANTONINUM.

Semen Cinæ.

Wormseed, as well as the santonin derived from it, almost always, when given in medicinal doses, gives rise to undesirable effects.

Neither santonin, which is insoluble in water, nor its soluble salt with soda gives a red color when mixed with alkalies. This occurs, however, when the drug is dissolved in alcohol and then precipitated with alkalies. Santonin undergoes similar changes in the human body to those produced on it by alcohol. After it has been taken in any form and in small doses (0.2 gramme [gr. iij] or more) after from two to three hours, the voided urine presents a yellow color, as if curcuma or chrysophanic acid had been added to it. White paper or linen soaked in it shows when dried, yellow spots, a fact first pointed out by Martin.* The addition to such urine of alkalies, such a soda-lye, ammonia, an alkaline carbonate, etc., causes as cherry-red color. The red color disappears spontaneously after from 30 to 36 hours, in contrast with the urine voided after the employment of rhubarb, the red color produced in which by alkalies, according to J. Munk,† is permanent. Further differences are noted by this author, the red discoloration of rhubarb urine disappearing under the action of reducing agents (zinc dust, sodium amalgam), while that of santonine urine resists these; baryta and lime water, also, added to the rhubarb urine throw down the chrysophanic acid with the precipitate, the red color of which is not removed by washing, while in alkaline santonine urine the pigment remains in solution under the same treatment.

Santonine urine, as opportunely discovered by L. Lewin, deflects the plane of polarization to the left. The changes which

*Martin, Buchner's N. Repert. f. Pharmacie, Bd. ii , 1853, H. 5.

†J. Munk, Virchow's Archiv, 1878, p. 136.

santonine undergoes in the system are unknown. It is held by Mialhe* that an oxidation product is formed having the peculiarities of a weak acid. The elimination of the same can be demonstrated in the urine after two or three doses of even 0.2 to 0.4 grammes (gr. iij to gr. vi). In the event of decomposition of santonine urine, the carbonate of ammonium, which is generated, produces in it a red color, which under certain circumstances, such as the existence of vesical catarrh, may cause it to be mistaken for bloody urine.

In some cases the ingestion of santonine has been observed to cause strangury and itching in the urethra.

Symptoms which are nearly as constant as those referable to the urine, are the disturbances of the sense of sight which manifest themselves after even small doses of santonine, changes which manifest themselves chiefly in yellow vision (chromatopsie) and which may continue for several hours. This symptom was first observed by Itzstein and afterwards by Spencer Wells. Rose† investigated this matter most carefully. According to him there occasionally appears before the peculiar yellow sight, after large doses of santonin, a violet color of the field of vision, the intensity of which color is in proportion to the darkness of the objects looked at. All lighter objects, such as windows, paper, etc., appear actually yellow. Red and blue appear often in their complementary colors, orange and green, so that carmine red appears pale, madder red, a bronze color, and the sky and blue objects green. This, however, is not always the case, and it has been noticed after the employment of santonin that red appears violet or light, and dark objects appear orange to one person and to another green.

This phenomenon is not due to a discoloration of the media of the eye by the products of the decomposition of santonine, after the manner of the action of the coloring matter of the bile in icterus, as was formerly believed to be the case, but is due, according to Rose, to a nervous change in the retina. M. Schultze‡ maintains that the yellow pigment of the macula lutea is changed by the action of santonin, and that it is thus that the vision becomes yellow. The complete absence of santonine in the media of the eye, as also the failure to detect the same by chemical means in the

*Mialhe, Comptes rendus xlvii., p. 413.

†Rose, Virchow's Archiv, Bd. xvi., p. 233 u. Bd. xviii., pag. 15.

‡M. Schultze, Ueber den gelben Fleck d. Retina, Bonn, 1866.

retina, renders a direct action of this substance on the parts which receive the impression of light improbable, but does not, as observed by Hermann,* exclude the possibility of its doing so, because of the fact that the changes are so slight and the quantity of the active substance may be so small as to elude detection by experiment.

Among other changes in the eyes Martin observed increased lachrymation and a sense of pressure, and others noticed a flickering before the eyes. While Rose, however, denies the occurrence of amblyopia and disturbances of accommodation, other authors, Bianchi–Cogliesi,† for instance, reports the occurrence of amaurosis, appearing in children after medicinal doses, and lasting for two and a half months.

Besides the eyes many persons experience also a distress in the stomach after the exhibition of santonin. Thus Martin noticed in his own person the appearance of nausea after taking 0.4 gramme (gr. vj) of santonine, and Rose observed vomiting after its employment. Associated with this there may also occur borborygmi and eructations.

Rose has also reported symptoms referable to the central nervous system, such as hallucinations of smell and taste, headache and a species of depression, symptoms denominated in their totality "Santonine intoxication."

Affections of the skin very seldom occur after the exhibition of santonin. Sieveking‡ has described a case of this nature. A child to whom 0.18 grammes (gr. iij) of santonin had been given for worms, vomited soon after taking the dose, whereupon an urticaria appeared over the entire body, but soon disappearing. The repetition of the same dose was followed by a recurrence of the general urticaria, and the entire skin, and particularly that on the eyes, nose, and lips, became so swollen and œdematous as to render the face completely unrecognizable. Salivation occurred simultaneously. The sensorium was not involved. The symptoms disappeared within an hour, under the influence of a warm bath.

*Hermann, Lehrbuch der Toxikologie, Berl., 1874, p. 384.
†Bianchi-Coglicsi, Refer. in Husemann, Pflanzenstoffe, Berlin, 1871, p. 928.
‡Sieveking, British Medical Journal, Febr. 1871.

BENZOLUM.

J. Munk* found, by experiments on himself, that benzole has a disagreeable, sharp burning taste and that its action in the mucous membranes is almost caustic. Commencing with 25 drops, he increased the amount to 50 drops in twenty-four hours. He found as a result of this a lasting sensation of fullness, oppression and burning in the epigastrium, and slight headache, while no marked effect was manifest on either the pulse or the respiration. The inhalation of benzole for anæsthetic purposes gives rise, according to Simpson,† to intolerable roaring in the head, and Richardson observed twitching of the muscles, dyspnœa and convulsions after such use of the drug.

A portion of the benzole is eliminated from the stomach in the form of gas, as is manifest in that the eructations, commencing with the exhibition of the substance and continuing for eight hours, have the odor and taste of coal tar. Another portion enters into a group of organic atoms to form the "phenol-forming substance."

In applying benzole externally to the genitals for the destruction of vermin care must be taken that it do not get in between the scrotum and the thigh. Applied to this or similarly sensitive surfaces, it causes extremely violent pain, which lasts for several minutes, and is followed by a more or less extensive eczema.

ACIDUM PICRICUM.

Picric acid, which has been recommended as an astringent and tonic, and also as an anthelmintic, occasionally, as stated by Seitz,‡ causes an icteric discoloration of the skin and conjunctiva.

*J. Munk, Pflüger's Archiv, Bd. xii., p. 147.
†Simpson, Monthly Journal of Medical Science, 1848 Apr.
‡Seitz, Deutsche Klinik, 1855, 40.

VI.—SUDORIFERA.

FOLIA JABORANDI.

Following the employment of jaborandi, the leaves of the pilocarpus pinnatus and simplex, nearly all observers have reported a series of unpleasant untoward effects as accompaniments of the normal action of the drug. The latter is the well known diaphoresis and subjective sensation of warmth which, within from ten to twenty minutes, follow the exhibition of an infusion of, for instance, 4 grammes (ʒ i) of the leaves. It first appears on the abdomen and breast, afterwards on the face, and later on both the lower and the upper extremities, and lasting for from about two to four hours. A secretion of viscid saliva, which occurs simultaneously, or somewhat earlier, continues for an equal length of time. The average loss of weight occurring from the perspiration is, according to Riegel*, 750 to 1000 grammes (1½ lbs. to 2 lbs.), but may exceed even 2 kilogrammes (4 lbs). The pulse becomes, shortly after the ingestion of the drug, more frequent and compressible, and later it frequently becomes small, with diminution in the force of the cardiac contraction, pallor of countenance, and a subjective feeling of chilliness. Among the untoward effects which have been observed, the first demanding notice is the vomiting which occurs in from half-an-hour to an hour after taking the drug, and which is always preceded by prolonged nausea. This is extremely distressing and exhausting to the patient, continues for a considerable length of time, and may readily lead to severe collapse. In forty-one observations, Riegel observed its occurrence in eighteen cases, while nausea without vomiting occurred ten times. Lohrisch† noticed the occurrence of severe vomiting twelve times, and of nausea twenty-two times, in thirty observations. The nausea sometimes occurred immediately after the exhibition of the drug, and again did not appear until half-an-hour or later. Bardenhewer‡ attributes the nausea and vomiting to the swallowing of the saliva, which is so freely secreted, and which, through being thus swallowed, irritates the mucous membrane of the palate, throat, etc.

*Riegel, Berliner Klin. Wochenschr., 1875. No. 46.

†Lohrisch, Berliner Klin. Wochenschr., 1875, No. 18, und Inaug.-Dissertat, Berlin, 1875.

‡Bardenhewer, Ueber die Therapeut. Wirkung des Jaborandi, Bonn, 1875.

Riegel concedes the explanation for a few of the cases only, as he has seen vomiting to occur in patients who have immediately expectorated the saliva.

Besides the nausea and vomiting, a desire to urinate is the most common occurrence, it supervening in about forty per cent. of all the cases. This occurs so suddenly and is so pressing as to be quite resistless. Occasionally there is also experienced a burning pain in the urethra and in the lumbar region, which is so severe as to force from the patient loud expressions of pain.

The frequent disturbances of sight, to which Martindale first called attention, also demand a notice. The patient complains of defective sight, because there seems to be a veil before his eyes. A few authors claim to have detected a contraction of the pupil with this condition, but Riegel was unable to corroborate this claim.

In addition to the untoward effects noted, there also occurred hiccough, vertigo, and headache with a species of stupor, and, in some patients, a greater or lesser degree of chilliness, and also gastric and abdominal pains, occurring towards the end of the sweating stage. These symptoms also disappear with the cessation of sweating. In very weakly persons collapse, without vomiting, is also occasionally observed

PILOCARPINUM MURIATICUM.

After the discovery of the pharmacological peculiarities of jaborandi, numerous experiments were instituted with a view to isolating its active principle, in the hope that its exhibition might secure the therapeutic action of the plant, without its untoward effects. It remained for Merck to derive from the plant the pure alkaloid, or its muriatic acid compound, a crystallizable, slightly bitter astringent substance, and soluble in its own weight of water.

Notwithstanding the fact that, in course of time, it has appeared that the use of this principle likewise gives rise to a series of unpleasant symptoms, its capability of exerting its action when administered subcutaneously vests it with such advantages over the jaborandi leaves as to give it the preference to the latter when used as a diaphoretic. According to the investigations of Weber*, one ccm. (16 minims) of

*Weber, Centralblatt f. d. Medicin, Wissenschaft, 1876, No. 44.

a two per-cent. solution of the muriate of pilocarpine is equal to an infusion of 5 grammes (gr. lxxv.) of jaborandi leaves in 120 grammes (℥ jv.) of water. The quantity of saliva secreted after an injection of pilocarpine varies, according to Losch*, with the individuality of the patient. The saliva itself is tough, viscid and often as thick as albumen. The occurrence of salivation follows diaphoresis immediately. The individuality of the patient also plays a rôle in this connection, some persons being bathed in perspiration through doses which in others cause only slight transpiration. During the secretion of perspiration chills occasionally occur. Consonant with these symptoms there is an acceleration of the pulse, of from thirty to forty beats per minute. Patients often complain of palpitation of the heart, and very sensitive persons of a feeling of anxiety, which, however, speedily disappears.

Vomiting occurs later on and when it once sets in it is very severe. According to Losch vomiting occurs in women once in five cases, and but once in ten in men. It is usually followed by collapse. Demme† saw in children, in addition to vomiting, debility nigh to fainting, pallor of countenance and distressing hiccough. A burning sensation was also experienced in the urethra or glans penis, ordinarily associated with a frequent desire to urinate. Federschmidt‡ also reports dysuria as manifesting itself in two cases. During the secretion of sweat and saliva, patients sometimes complained of a sensation as if the bladder were full of water and they found it impossible to void it. These abnormal sensations failed to appear after subsequent injections.

Another symptom equally worthy of note is the characteristic disturbance of sight manifesting itself as mistiness of vision. This becomes so intense in some persons of perfectly normal focal distance and acuteness of vision that they are unable, as Losch declares, to read large print at a greater distance than six inches. The symptoms occurred also in cases in which there was not the slightest increase in the quantity of tears secreted.

The most unpleasant of all the untoward effects, however, is the collapse which frequently occurs alike during the stage of secretion and after it, and even in robust persons. The greatest caution must

*Losch, Deutsches Archiv für Klin. Medicin, xxi., p. 258.

†Demme, Centralzeitung für Kinderheilkunde, 1877, No. 1.

‡Federschmidt, Zur Wirkung des Pilocarpin. muriatic. Erlangen, 1877

be exercised against this symptom during the exhibition of pilocarpine, inasmuch as a disregard for the possibility of its occurrence is apt to result disastrously. In the same manner regard must be had to the well-established excessive acceleration of the heart's action, which is often accompanied by absence of rhythm, and particularly in persons suffering from organic lesion of this organ.

An observation of Ranneft* may also be mentioned here: In the case of a uræmic patient the hypodermic injection of 0.02 gramme (gr. $\frac{1}{3}$) of the muriate of pilocarpin, was followed, the next morning, after the diaphoresis had subsided, by a swelling of the size of a fist of the submaxillary glands and a swelling also of the parotids and tonsils, with absence of fever. Under the influence of atropia these symptoms disappeared in the course of a day.

Great danger attends the untimely exhibition of pilocarpin in convulsions. Sänger† reports three cases of this nature, in which the injection of 0.02 gramme (gr. $\frac{1}{3}$) of pilocarpin was followed by œdema of the lungs. In one case the subcutaneous exhibition of 0.0006 gramme (gr. $\frac{1}{100}$) of atropia, as an antidote, saved the patient's life, but the two other cases proved fatal. Sänger accounts for this deleterious action by the deficient expectoration of the masses of mucus thrown off under the influence of the pilocarpine and by their entrance into the lungs. It is impossible for the patient to expectorate, because of the unconsciousness and suspension of reflex irritability resulting from the convulsions.

The fact that a number of observers have noted the symptoms above mentioned, and that, too, notwithstanding that they all employed the same preparation, excludes the supposition that the quality of the drug was responsible for them. It appears as if they are due to a certain predisposition on the part of the patient, and in many cases also, perhaps, the improper size of the dose is responsible. In regard to the latter, Leyden‡ and Curschmann,§ also maintain that the collapse which is occasionally observed may be obviated by a very gradual increase in the size of the dose. In general, however, in the light of experience, we are unable to prevent the deleterious untoward effects, and we are obliged to

*Ranneft, Jahresbericht f. d. ges. Medicin, von Virchow-Hirsch, 1877, II., p 437.
†Sänger, Archiv. f. Gynäkolog. Bd. xiv., H. 1.
‡Leyden, Berliner Klin. Wochenschrift, 1878, No. 27 u. 28.
§Curschmann, Eod. loco No. 25.

content ourselves by combating them as soon as possible after their appearance.

Atropia occupies the first place among the drugs employed for this purpose, inasmuch as it checks both the diaphoresis and the salivation, and as it also allays the painful sensations and the vomiting. It is administered either hypodermically (atropiæ sulph., 0.1 gramme [gr. jss] water 20 grammes [ʒ v] of which inject from five to ten drops) or per os (atropiæ sulph. 0.01 gramme [gr. $\frac{1}{6}$], water 20 grammes [ʒ v], of which give from twenty to thirty drops every two hours, until the symptoms have been allayed.) The bromhydrate of homatropin has been proven by Fronmüller, of service as an antidote to pilocarpine and has been recommended by him as such. He injects it subcutaneously in doses of 0.015 gramme (gr. $\frac{1}{4}$.) Collapse may be forestalled by the exhibition of stimulants. Demme (l. c.) claims to have obviated all the deleterious untoward effects liable to follow the injection of pilocarpin, by giving cognac before the operation. It is, in general, preferable to administer pilocarpin before rather than after the principal meal, and in view of the numerous observations of the great liability to collapse in patients suffering from valvular insufficiency, to regard heart disease as a contraindication for the use of the drug. Ohms* also regards pilocarpin as contraindicated in ulcer of the stomach and typhoid fever, because of the danger of hæmorrhage from the great dilatation of the vessels under the influence of the drug.

*Ohms, Petersburger medic. Wochenschr. 1878, No. 6, p. 50.

EMOLLIENTS.

GLYCERINUM.

The healing action of glycerine on wounds, demonstrated particularly by the experiments of Demarquay,* not infrequently fails to manifest itself, a directly opposite effect, indeed, taking its place. The impurity of the glycerine is assigned as the cause of this untoward action. This application of an impure preparation to the surface of wounds, eruptions of the skin, etc., give rise to a burning sensation at the point of application which lasts for several hours, and to a feeling of increased heat. The affected part at the same time becomes swollen. Moist eruptions secrete more freely, and under certain circumstances a pustular eruption is developed.

Chemically pure glycerine when applied to wounds causes only a temporary burning, due, probably, to its property of abstracting water from the parts. It is necessary in using this drug to bear in mind the fact that its sp. gr., according to Phar. Germ., is from 1.23 to 1.25. Preparations more highly concentrated than this are to be avoided in therapeutics, because of their irritating properties.

VASELINUM.

Vaseline recently introduced as a basis for ointments and as a vehicle for various substances, may by its application to the skin excite various degrees of inflammation. Lewin observed in his own case that the inunction of it upon a circumscribed spot on the forearm, excited an eruption of superficial papules, characterized by intense itching and confined to the seat of the application of the vaseline. It persisted for some ten or twelve days, and disappeared with desquamation. Other authors have also observed the appearance of inflammatory action on the hands and face after the inunction of vaseline.

*Demarquay, De la Glycerine, Paris, 1867.

OLEUM MORRHUÆ.

The peculiar, repugnant smell and taste of cod-liver oil, causes at first in different persons, usually adults, either during or subsequently to its exhibition, nausea and even vomiting, symptoms which do not, however, supervene after the oil has been used for a length of time. The administration of excessive doses is followed by diarrhœa. In addition to this cod-liver oil occasionally gives rise to eczema after it has been used for several days. This observation of S. Bennet* is explained by the fact that after large doses of cod-liver oil the skin gives off the peculiar odor of the volatile fatty acids of the oil. These, while circulating in the system also reach the skin, and there cause the eruptions probably by direct irritation. These, according to Duclos† are always of a vesicular nature and spread over the entire body.

*Bennet, Treatise on the Oleum Jecoris Aselli, London, 1841, p. 16, and 47.
†Duclos, Journal de Médicine. Sept.-Novem., 1846.

Rubefacients and Vesicants.

CHLORINUM.

Aqua Chlorinata.

Chlorine gas is irrespirable. Even in considerable dilution with atmospheric air it is an energetic irritant to the mucous membrane of the air-passages, causing increased secretion, nasal catarrh, cough, constriction of the chest and symptoms of actual bronchitis.

The effect of the gas on the skin is to cause a pruritic erythema, which disappears after a time with desquamation. In dilution it also, according to Schuchardt,* excites prickling and piercing sensations in the skin, which is sensitive and may take on a papular eruption, which disappears in branny desquamation.

CANTHARIDES.

Tinctura—Unguentum—Emplastrum Cantharidum.

The internal exhibition of cantharides or its tincture, in medicinal doses, excites a number of untoward effects, which take on different degrees of intensity according to the individuality of the patient. A burning sensation is experienced in the primæ viæ. After a time there is a pressing desire to urinate, a burning sensation in the urethra, and frequent and painful erections. The latter symptom may, as a result of the prolonged use of small doses, as also through increase of the dose within ordinary limits, give rise to threatening symptoms. The mucous membranes of internal organs take on a greater or lesser degree of inflammation, manifesting itself, as regards the stomach and intestines, in nausea, vomiting and diarrhœa, and as regards the urinary passages in increased frequency of desire to urinate, the urine occasionally containing blood, albumen or morphological constituents, and on the part of the genital apparatus, painful chordee.

The skin also is occasionally attacked with exanthematic

*Schuchardt, Arzneimittellehre, Braunschweig, 1858, p. 198.

changes, manifesting themselves as erythematous or papular eruptions.

More important than these effects following the internal exhibition of cantharides is the knowledge of those which result from its outward application. These symptoms following the application of a fly blister, which correspond with those already described, may result from the absorption of the active principle of the cantharides. Thus Ledelius,* among others, noticed vomiting, strangury and fever, to set in after a blister had been applied for three hours. · These symptoms, caused by absorption, are intense in proportion to the deviation of that portion of the skin to which the drug is applied, from its normal activity.

The treatment consists in the speedy removal of the blister and the cleansing of the skin with soap. Mucilaginous drinks should be given to allay the irritation of the internal organs.

FABA ANACARDII.

The anacardium bean, vulgarly known as cashew nut, contains in its capsule a reddish-yellow substance, cardol, soluble in ether, alcohol, etc., which Frerichs has recommended as preferable, under certain conditions, to cantharides, as a vesicant. Cardol derived from anacardium occidentale is known as cardoleum vesicans, that from semecarpus anacardium as cardoleum pruriens. The latter, owing to its liability to cause dermatitis, and even erysipelas, is not fit for use. But the anacardium occidentale is also often not limited in its sphere of action, diffuse inflammatory œdema and also eczema occurring on remote parts, as, for instance, the face, being liable to follow its application.

While this preparation is seldom employed by physicians, the anacardium bean is frequently employed in domestic practice and thus gives rise to its typical affections of the skin. Thus E. Schwerin noticed it to produce erysipelas, spreading to an enormous extent in a woman who had introduced half a bean into her ear for the relief of a toothache and pain in the face. The face was bloated, the eyelids on both sides infiltrated with serum, the ear, cheek and forepart of the neck as far as the clavicle, swollen and

*Ledelius, Refer. bei. Wibmer, Wirkungen der Arzneimittel, Bd. III., p. 252.

reddened. The external, auditory canal, the external ear, and the surrounding integument were covered with vesicular crusts. Recovery followed in a few days.

In another case an anacardium bean perforated longitudinally, and strung on a thread was worn around the neck for a pain in the breast, in such a manner that the bean laid on the manubrium of the sternum. Two days later an erysipelas developed which spread over the entire front of the chest, the mammæ, and the neighborhood of the shoulders as far as the lower jaw, and was dotted with numerous vesicles.

According to Bazin* the oil expressed from the pericarp of the bean, if brought in contact with the skin may also cause the appearance of one or more vesicles containing purulent matter, within from six to twenty four hours.

CORTEX MEZEREI.

Mezereon, which is still occasionally employed as a vesicant or is applied to establish superficial issues, causes vesicles on the skin which may develop into ulcers. The latter are very painful, heal extremely slowly, and are frequently surrounded by a pustular eruption.

After the occurrence of the inflammatory symptoms, symptoms of general poisoning and even death may occur from absorption of the drug. Pluskal† observed a case of this nature. It was attended by headache, dryness of the throat, an irritative cough, fever, unconsciousness, convulsions, and finally death.

SUMMITATES SABINÆ.

The external application of the powdered tops of savin for the cauterization of condylomata, gives rise occasionally to such intolerable pain as to necessitate the discontinuance of the application.

Following the internal use of small and medium doses (0.3 to 0.8 gramme [gr. v to gr. xij]) as an emmenagogue, there is disturbance of digestion, occasional vomiting and diarrhœa, desire to urinate, and, during menstruation, a profuse discharge of blood. In

*Bazin, l. c., p. 119.

†Pluskal, Oesterreische medic. Wochenschr., 1842, No. 18 und 1844, No. 50

pregnant females large doses or the prolonged use of small doses may induce abortion. The oil of savin is more energetic in its action than the herb.

PETROLEUM.

The external application of petroleum may give rise, in a short time, to a dermatitis. Hillairet made some observations to this effect, which have been reported by Crucis.* According to these there appeared on different persons who had received petroleum embrocations, and shortly after the application, on the abdomen, thighs, and partially also on the legs, an eruption of confluent vesicles on an inflamed groundwork, but showing no induration. Notwithstanding the suspension of the embrocations there appeared daily for eight days a fresh crop of vesicles. An additional application made on the ninth day was followed by no fresh eruption.

In other persons the symptoms of systemic disturbance were more prominent, the local symptoms being limited to violent irritation. The constitutional symptoms may consist of a prolonged sensation of dizziness, frontal headache, symptoms of slight intoxication, nausea and vomiting.

CHRYSAROBINUM.

Goa Powder.

"Araroba powder or goa powder" has long been used in England, Brazil and the East Indies, as a secret remedy in the treatment of affections of the skin. The tree whence is derived the powder is most common in the province of Bahia. Araroba is found as a sulphur-yellow powder in the crevices and cavities which traverse the tree in the direction of its transverse diameter.† According to an earlier analysis the powder contains 84 per cent of chrysophanic acid. Liebermann,‡ however, showed that the substance recovered from goa powder by extraction with benzole is not chrysophanic acid, but, according to his chemical synthesis, a body of different composition to which he gave the name of chrysarobin.

*Crucis, Action physiologique et Morbide de la Térebinthine et de quelques autres Hydrocarbures, Paris, 1874, p. 29.

†Vierteljahrschr. f. Dermatol. u. Syphilis VI., 1879, p. 385.

‡Liebermann, Berichte der deutsch. chem. Gesellsch., Jahrg. XI., p. 1603.

Chrysarobin may be converted into chrysophanic acid by the action of potash-lye and exposure to the air. Experiments of L. Lewin* and Rosenthal have established the fact that chrysarobin suffers similar changes in the bodies of animals. Chrysophanic acid may be detected in the urine after either the internal or the external exhibition of the drug.

Balmanno Squire† first employed this drug in the form of ointment in psoriasis and later in eczema, acne, etc., with good results. Numerous therapeutic experiments were afterwards made with chrysarobin, in Germany. The ointment is usually applied to the skin, previously cleansed of the psoriatic scales by either mechanical or chemical means (spirit of soap, etc.).

All observers who have employed chrysarobin report unpleasant local and systemic untoward effects from its use. Kaposi‡ has described them most minutely. The rubbing of chrysarobin upon a psoriatic spot is followed by inflammation at the point of application, occurring earlier in some and later in others, and liable to spread extensively over the sound skin. Some persons manifest a peculiar predisposition to this action, in which cases the inflammation is unusually intense as to duration and extent. The face and genitals are peculiarly susceptible to the irritation of chrysarobin ointment.

According to Kaposi there are three forms of inflammation:

1. A diffuse inflammatory redness and swelling. In some persons this occurs as a halo of varying breadth around each psoriatic patch, after from four to six applications, and in others after from eight to fifteen. This redness disappears, in the desquamation of the epidermis, in from ten to fourteen days after the discontinuance of the application. Frequently, however, the inflammation and swelling continue to spread in spite of the suspension of the drug, and is attended by pain, fever, sleeplessness, swelling of the glands, etc.—in short, the general symptoms ensuing on an attack of diffuse dermatitis.

2. The inflammation may manifest itself also in the appearance of reddish brown, firm papules, of pin-head size, some of which also take the form of vesicles and pustules. They correspond to the outlet of follicles, and the patient complains of an annoying itching and burning sensation.

*L. Lewin und O. Rosenthal, Virchow's Archiv. Vol. 85, 1881.

†Balmanno Squire, British Medical Journal, May and November, 1877

‡Kaposi, Wiener medicin, Wochenschrift No. 44.

3. Painful furuncles may also occur. Cold water compresses have been recommended for the relief of the pain and inflammation. Neumann recommended as a prophylactic measure against this irritation of the skin, the protection of the circumference of the diseased parts with adhesive plaster. Others believe that these effects may be guarded against by gradually increasing the strength of the chrysarobin ointment. Kaposi discountenances the use of chrysarobin on the face, and permits its application to the genitals only after careful isolation of the adjoining folds of skin, and advises the suspension of the drug as soon as an areola appears around the psoriatic patches.

As an accompaniment of the inflammatory complications mentioned, the drug nearly always causes a discoloration of the tissues with which it comes in contact. The sound skin, as well as the nails, assume a reddish or violet-brown aspect, and the hair a golden-yellow or variegated greenish color. The contact of soap with the parts thus changed as to their normal color, causes a change to a dark violet, through the action of the potash on the chrysarobin. This change of color is most marked in the inflamed areola which surrounds the psoriatic patches. The body linen also in the same manner as the skin becomes spotted to a greater or less extent, of a brown or violet color, and these spots are very hard to erase.

NAPHTOLUM.

Naphtol, a colorless, crystalline substance, soluble in alcohol, oils and fats, recommended by Kaposi* as a substitute for tar in different diseases of the skin, gives rise by repeated applications of a 10 to 15 per cent. solution, to a burning sensation at the seat of embrocation, which may continue from a quarter of an hour to an hour, without, however, the slightest appearance to indicate the existence of this condition.

Naphtol is absorbed by the skin and is eliminated with the urine. Larger quantities of the substance taken into the circulation are poisonous, according to Neisser.† He is convinced, from experiments on animals, that large doses of naphtol give rise to hæmaturia, through destruction of the blood. He recommends, for this reason, circumspection as regards the dosage, and avoidance of the drug in existing nephritis.

*Kaposi, Wien. Med. Wochenschr. 1881, No. 22–24.

†Neisser, Centralbl. f. d. Med. Wissenschaft. 1881, No. 30.

Kaposi himself observed hæmaturia, symptoms of Bright's disease, ischuria, vomiting, unconsciousness and eclamptic attacks in a boy, after the external application of naphtol.

ACIDUM PYROGALLICUM.

Pyrogallic acid was introduced by Jarisch* as a remedy in the treatment of cutaneous affections. The untoward effects which manifest themselves after its employment are not important. Applied to the sound skin or to psoriatic patches it causes a brownish discoloration. On the extremities it excites localized inflammation which may develop into vesicles and desquamation of the skin. Applied to firm, infiltrated patches, the ointment causes deep destruction of the skin, even as far as the corium. The cicatrices left after the cauterization of lupus nodules are smooth, white and pliable. Jarisch observed, as a result of the application of the acid in eczema marginatum, pain lasting for several days and suffering aggravation, particularly on the removal of the dressing.

On the strength of the observations of Jarisch,* Neisser† also tried the pyrogallic acid in the case of a man afflicted with psoriasis universales. In order to compare their respective effects, the upper and lower extremities of the right side and the back were energetically rubbed with unguentum rhei (ext. rhei spirit, as a 20 per cent. ointment), the left side and breast being similarly treated with ointment of pyrogallic acid. The parts thus anointed were then covered with a thin layer of the respective ointments, and the whole body enveloped in gummed paper, which was secured by means of a roller bandage. In a few hours after this operation rigors set in, with diarrhœa and vomiting, which continued for three days, when they were followed by collapse and death. The urine contained the coloring matter of blood. The autopsy revealed the causes of death to be decomposition of blood, nephritis hæmaglobinica and desseminated fatty degeneration of the heart.

Doubtless the majority of these symptoms were due to suppression of the cutaneous perspiration, inasmuch as the effect of such an extensive inunction must be identical with that of covering the body with a coating of varnish.

*Jarisch, Wiener Medic. Jahrb. 1878, H. iv.
†Neisser, Zeitschr. f. Klin. Medicin. Bd. i., Heft. 1.

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☞Page proofs REVISED and APPROVED by the Author.☜

THE UNTOWARD EFFECTS OF DRUGS,

A PHARMACOLOGICAL AND CLINICAL MANUAL.

— BY —

DR. L. LEWIN,

Docent of Materia Medica, Hygiene and Public Health in the University of Berlin.

—o—

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—o—

Second Edition, revised and enlarged. The only English translation having the author's endorsement.

—o—

DETROIT, MICHIGAN:

Geo. S. Davis, Medical Publisher.

To the Medical Profession:

In issuing my edition of Dr. Lewin's work on "The Untoward Effects of Drugs," I am constrained, through circumstances, to offer some explanation for my placing on the market a second translation so shortly after the one issued by another publishing house: I had completed arrangements with Dr. Lewin for bringing out this book on this side of the Atlantic, and had committed the work of translation, some time before any intimation of another translation was made. On receiving notice that others had assumed to issue the work in this country, I was naturally, in view of my contract with the author, very much surprised, and wrote to Dr. Lewin for an explanation. The following is a copy of his reply:

Berlin, April, 17, 1882.

Mr. Geo S. Davis,
Medical Publisher,
Detroit, Mich., U. S. A.

DEAR SIR:—Your communication has been received. It is with profound indignation that I learn that an unauthorized edition of my work "Die Nebenwirkungen der Arzneimittel" (A. Hirschwald, Berlin, 1881), is about to appear in America. I beg herewith to affirm that you alone are authorized to have this work translated into the English language, and to publish and sell such English translation in America. I have agreed to revise the translation which you are to issue, and to make such additions as the progress of the same shall render necessary up to the time of publication. The translation to be issued by you is the only one having my endorsement, and being prepared under my supervision, I respectfully ask for it the attention of the medical profession of America.

I remain with great respect,
Yours very truly,
DR. L. LEWIN,
Docent of Materia Medica, Hygiene and Public Health in the University of Berlin.

The facts of the case, in connection with the two translations now in the market, are thus succinctly stated. They are their own comment, and scarcely call for further emphasis.

Of the merits of Dr. Lewin's work on "The Untoward Effects of Drugs," it is not necessary to speak. It has received the universal commendation of the medical press of Germany, and has taken a high place among medical publications. Its peculiar merit is the fact that it is the only work especially devoted to the subject of which it treats.

In lieu of the many complimentary press notices which it has received, I submit herewith an extract from an extensive review in the Zeitschrift für Klinische Medicin, written by Rossbach, Professor der Arzneimittellehre in dem Institut für Experimentelle Pharmakologie der Universität Würzburg, an authority whose opinion will be accepted without question :

"It appears from the foregoing that no small amount of credit is due the author for imposing on himself the great task of collecting and clearly summarizing the material which existed previously as scattered, and often mentioned merely incidentally, in a multitude of published articles. That this has been an exceedingly tedious task is manifest from the completeness of the facts which have in this manner been rescued from forgetfulness, and which must awaken the keenest interest not only in the practicing physician but also in the professional pharmacologist, and which I am convinced will stimulate to many new observations and experiments. The author first and very properly aims to collect all observations which had been previously made. A criticism of these is impracticable, both owing to lack of time and to deficiency in the necessary kind of knowledge ; in order to give a critical sifting of these, they must from this time on be subjected to frequent deliberate observations, and viewed from all sides. Any criticism based on a defective foundation must be shallow and destructive rather than edifying ; it is permissible only in cases in which the author has considered matters which are somewhat doubtful, and has left their confirmation for time to establish.

It has, unfortunately, not been possible in this reference to give more than an approximate conception of the richness of the contents of the book ; it must suffice to state that all the drugs in general use are, without exception, investigated in reference to their untoward effects, and that the reporter has not been able to establish an exception in the case of a single drug.

No physician will be able to lay down the book without having received from it the richest information, and without having incited in him an impulse to further observation."

Of the translation it is only necessary to state that it has been pronounced by the author to be "ausgezeichnet" (superior).

The book will be mailed, postage prepaid, on receipt of $2.00.

GEORGE S. DAVIS,

P. O. Box 470. *Medical Publisher, Detroit, Mich.*

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